Republic of Yemen
Sana'a University
Faculty of Medicine

Notes On

Practical Pharmacology

for medical students

Done By:

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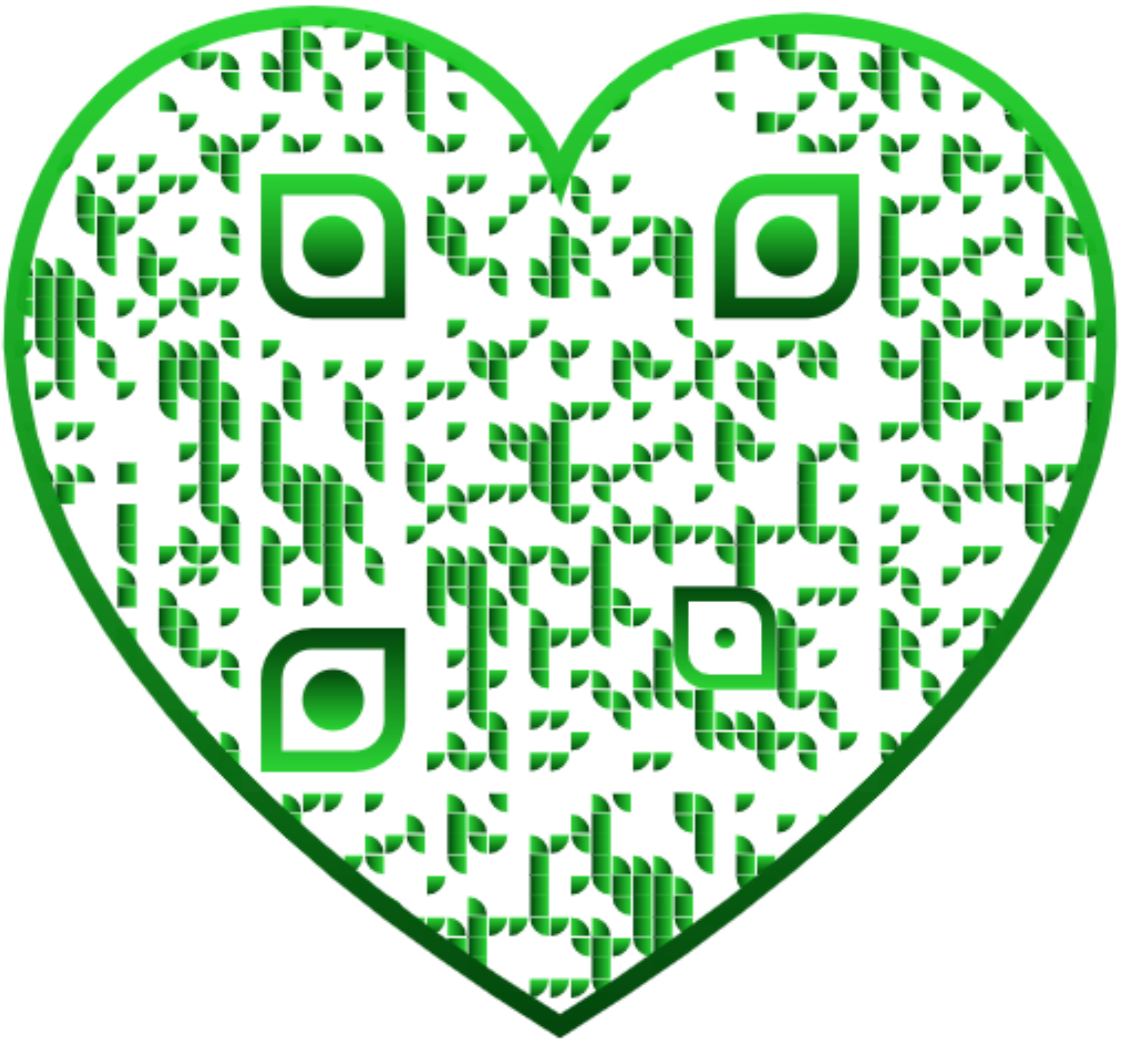

Second Edition

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Dedication to

Our families,

for their endless love, support and encouragement throughout our life.

Our professors,

for their guidance, support and confidence in us. You were such wonderful motivators even when the coping seemed tough for us. We aspire to emulate you.

Our team, IMS team,

who have supported each other throughout the process.

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Preface

•This laboratory book represents a blend of ideas from other laboratory manuals, text books and one's past experience in pharmacology laboratories. This book is prepared for the third year students of medicine.

•This book was done by Dr. Mamdouh A. Sonbul & IMS team who have worked together to build an accurate, up-to-date, and visually appealing illustrated book.

•They have attempted to maintain the highest standards of excellence and accuracy. At the same time, they have been attuned to the evolving needs of students in the practical pharmacology.

•Any suggestions, remarks or criticism will be greatly welcomed, heartily appreciated and very much considered.

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GENERAL OBJECTIVES OF THIS BOOK

At the end of the practical training in general, experimental and clinical pharmacology the learner shall be able to:

- List the various dosage forms and enumerate their advantages and disadvantages.
- Advise patients about the proper use of medication devices, storage of medicines etc.
- Retrieve drug information from appropriate sources.
- Order monitoring of drug levels where indicated and take appropriate remedial measures.
- Appreciate the importance of adverse drug reaction monitoring and its contribution to rational therapeutics.
- Prescribe rationally and in an individualized pattern.
- Plan and carry out experiments to demonstrate the effect of drugs in experimental animals and isolated tissues.
- Advise dosage modifications in special situations such as liver and kidney failure, pregnancy and lactation and in children.

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Section One

GENERAL PHARMACOLOGY

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Dosage Forms

- **Definition:** Dosage forms are the means (or the form) by which drug molecules are delivered to sites of action within the body.
- **The need for dosage forms:**
  - Accurate dose.
  - Protection e.g. coated tablets, sealed ampules.
  - Protection from gastric juice.
  - Masking taste and odour.
  - Placement of drugs within body tissues.
  - Sustained release medication.
  - Controlled release medication.
  - Optimal drug action.
  - Insertion of drugs into body cavities (rectal, vaginal)
  - Use of desired vehicle for insoluble drugs.
- **Classification:**

❖ **Oral Dosage Forms:** are classified into solid and liquid dosage forms.

➢ **Solid Forms:**

- Powder:
  - Intimate mixtures of dry finely divided drug or chemicals intended for internal or external use.
  - The mixed powders may be stored in dry form and mixture prepared by the pharmacist when required for dispensing, by suspending the powders in the appropriate vehicle.

  - **Bulk Powders** are multi-dose preparations consisting of solid, loose, dry particles of varying degrees of fineness. Contain one or more active ingredients, with or without excipients and, if necessary, coloring matter and flavoring substances.

  - Usually contain non-potent medicaments such as antacids since the patient measures a dose by volume using a 5 ml medicine spoon. The powder is then usually dispersed in water or, in the case of effervescent powders, dissolved before taking.
  - Examples of drugs administered by this route: e.g. uresoda and antiacid.

✓ **Advantages:**

- Good chemical stability compared with fluids.
- Powders are in the form of small particles; they offer a large surface area and are **rapidly dissolved** in the gastrointestinal (GI) tract. Drugs that have to be given in bulk can be best administered in powder form by mixing them with foods or drinks.
- Convenient for large dose.
- Manufacturing of powder is economic hence product cost is quite economic as compare to other dosage form.
- Easy to swallow even in large bulk, especially if mixed with drink food (useful for stomach-tube feeding)
- It gives the quick onset of action.

- The smaller particle size of powders causes more rapid dissolution in body fluids, increases drug bioavailability, and decreases gastric irritation compared with tablets

✕ **Disadvantages:**

- Less accuracy in dispensing potent drugs in powder dosage form.
- Patient may misunderstand the correct method of use.
- The masking of unpleasant taste is a big problem.
- Not suitable for hygroscopic substances, deliquescent (tending to melt or dissolve in humid environment), or aromatic materials.
- Time-consuming to prepare.
- We cannot supply drugs in powder dosage form which are degraded in the stomach.

- Tablets:
  - A tablet is a hard, compressed medication in round, oval or square shape. Solid dosage form containing unit dose of one or more medicament.
  - Prepared by mould method or compression method.
  - The **excipients** include:
    - Binders, glidants (flow aids) and lubricants to ensure efficient tabletting.
    - Disintegrants to ensure that the tablet breaks up in the digestive tract.
    - Sweeteners or flavours to mask the taste of bad-tasting active ingredients.
    - Pigments to make uncoated tablets visually attractive.

  - A **coating** may be applied to:
    - Hide the taste of the tablet's components.
    - Make the tablet smoother and easier to swallow.
    - Make it more resistant to the environment.
    - Extending its shelf life.
  - Examples of drugs administered by this route: e.g. Bigel plus & Biomol

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✓ **Advantages:**

- Tablets are elegant in appearance and convenient to use.
- The tablets dosage form are simple, economical in manufacturing, **most stable** and most convenient in packaging, shiping and transportation.
- Unit dosage forms with accurate, stable dose and great precision and least variability.
- Cheapest oral dosage form.
- A wide range of tablet types is available, offering a range of drug release rates and durations of clinical effect. Tablets may be formulated to offer rapid drug release or controlled drug release, the latter reducing the number of daily doses required (and in so doing increasing patient compliance).
- Tablets may be formulated to contain more than one therapeutic ingredients showing a combination thus reducing multiple tablets use.
- It is very easy to mask the taste of bitter active ingredients thus make convience for patient.
- Tablets provide accurate dosage to the patient.
- Tablets are generally an inexpensive dosage form.
- Low manufacturing cost as compare to other solid dosage forms and large scale production is possible.
- Objectionable odour and bitter taste can be masked by coating technique.
- Easy to divide into halves and quarters whenever fraction dose is required.
- Lighter and compact.

✕ **Disadvantages:**

- Its manufacturing involve several unit operation thus at each step there is loss of ingradients of tablets
- May be problematic for children and elders due to difficulties in swallowing.

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- Slow absorption i.e. the absorption of therapeutic agents from tablets is dependent on physiological factors, e.g. gastric emptying rate and shows interpatient variation.
- Drugs with poor wetting, **slow dissolution**, intermediate to large dosages may be difficult or impossible to formulate and manufacture as a tablet that provide adequate or full drug bioavailability
- Some drugs resist compression into dense compacts, owing to amorphous nature, and low density character.
- Hygroscopic drugs are not suitable for compressed tablets.
- Sensitive to oxygen drugs may require special coating.

- Buccal and sublingual tablets:
  - Sublingual and buccal medications are administered by placing them in the mouth, either under the tongue (sublingual) or between the gum and the cheek (buccal).
  - The medications dissolve rapidly and are absorbed through the mucous membranes of the mouth, where they enter into the blood stream.
  - Avoid the acid and enzymatic environment of the stomach and the drug metabolizing enzymes of the liver.
  - Examples of drugs administered by this route: e.g. vasodilators, steroidal hormones.
  - Examples of drugs administered by this route: e.g. Nitroglycerin.
    - ✓ **Advantages:**
      - The medication **absorbs quickly**, these types of administration can be important during emergencies when you need the drug to work right away, such as during a heart attack.
      - These drugs do not go through the digestive system, so they aren't metabolized through your liver (no first pass effect). This means you may be able to take a lower dose and still get the same results.
      - It is easier to take for people who have problems swallowing pills.
      - Higher bioavailability and onset of action compare to oral route.
      - Rapid absorption due to high vascularization beneath the tongue.

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- Reduce the side effect due to low dose and high efficacy.
- Provide fast dissolution or disintegration in oral cavity without water or chewing action.
- pH in the mouth is relatively neutral so drug will be **more stable**.

✕ **Disadvantages:**

- Eating, drinking, or smoking, can affect how the drug is absorbed and how well it works.
- This route is generally considered unsuitable for prolonged administration.
- Any open sores in your mouth can also become irritated by the medication.
- Only small doses can be accommodated easily.
- Not suitable for sustain release formulations.
- It cannot be used when patient is uncooperative or unconscious.

***Note:** The patient should not smoke while taking sublingual medication, because smoking causes vasoconstriction of the blood vessels. This will decrease the absorption of the medication.

- **Chewable tablets:**
  - They are tablets that chewed prior to swallowing.
  - They are designed for administration to children e.g. vitamin products.
  - Examples of drugs administered by this route: e.g. Acicone-S

✓ **Advantages:**

- It is given for children and it looks like sweets or candies.

✕ **Disadvantages:**

- Tablet should be chewed in mouth before swallowing, otherwise it can't be absorbed.

- Capsules:
  - A capsule is a medication in a gelatin container.
  - Main advantage: mask the unpleasant taste of its contents.
  - The two **main types** of capsules are:
    - **Hard-shelled capsules**, which are normally used for dry, powdered ingredients.
    - **Soft-shelled capsules**, primarily used for oils and for active ingredients that are dissolved or suspended in oil.
  - Examples of drugs administered by this route: e.g. Pharmaton, Vitamin E, Prostavital, Stimulan, Foracort 100, Wantex & Urinex.

✓ **Advantages:**

- Neat and elegant in appearance (attractive in appearance).
- The drugs having unpleasant odor and taste can be administered by enclosing them in a tasteless shell.
- The ready solubility of gelatin at gastric pH provides rapid release of medication in the stomach.
- Since hard gelatin capsules may be compounded by the pharmacist, this dosage form offers physician's greater flexibility in dosages and drug combinations than is available with prefabricated medication.
- They are smooth, become very slippery when moist and can be easily swallowed.
- They are economical.
- They are easy to handle and carry.

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- Capsules are made from gelatin and hence they are therapeutically inert.

✕ **Disadvantages:**

- Capsules are not suitable containers for liquids that dissolve gelatin, such as aqueous or hydroalcoholic solutions.
- Very soluble salts, such as bromides or iodides should not be dispensed in capsules, as the rapid release of such materials may cause gastric irritation.
- The hygroscopic drugs cannot be filled in capsules. They absorb water present in the capsule shell and hence make it very brittle, which ultimately breaks into pieces.
- The concentrated preparations which need previous dilution are unsuitable for capsules because it may lead to irritation in stomach if administered as such.

- **Effervescent tablets:**
  - Effervescent tablets are uncoated tablets that generally contain acid substances (citric and tartaric acids) and carbonates or bicarbonates and which react rapidly in the presence of water by releasing carbon dioxide.
  - They are intended to be dissolved or dispersed in water before use providing:
    - Very rapid tablet dispersion and dissolution.
    - Pleasant tasting carbonated drink.
  - Examples of drugs administered by this route: e.g. Calcium.

✓ **Advantages:**

- Improved taste
- Faster absorption
- Presentable fizzy tablets.

✕ **Disadvantages:**

- Larger tablets
- Complex production process
- Delicate packaging process.

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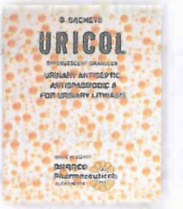
- Granules:
  - They are consisting of solid, dry aggregates of powder particles often supplied in single-dose sachets. They are irregular shape particle which are made to improve flow property of powder.
  - Some granules are placed on the tongue and swallowed with water, others are intended to be dissolved in water before taking.
  - Effervescent granules evolve carbon dioxide when added to water.

✓ **Advantages:**
- Rapid absorption.
- Masking of taste and smell.

✕ **Disadvantages:**
- Not stable after dissolution.



- Effervescent granules:
  - Granules of a varying size prepared with citric acid and tartaric acid which are responsible for the raise of Co_2, intended to be dissolved in water before swallowing.
  - Examples of drugs administered by this route: e.g. Uricol & Rani 150

- Lozenge:
  - It is a solid preparation consisting of sugar and gum, the latter giving strength and cohesiveness to the lozenge and facilitating slow release of the medicament.
  - It is used to medicate the mouth and throat for the slow administration of indigestion or cough remedies.
  - Examples of drugs administered by this route: e.g. COOL-X

✓ **Advantages:**
- Easy to compound and administer.
- Keeps the drug in contact with the oral cavity for an extended period of time.
- Local effect.

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- Has demulcent (soothing) effect on a sore throat since ingredients spread uniformly over affect mucosal membrane.

✕ **Disadvantages:**

- Looks like candy.
- Precaution with children.

- **Pastilles:**
  - They are solid medicated preparations designed to dissolve slowly in the mouth. They are softer than lozenges and their bases are either glycerol and gelatin, or acacia and sugar.
- **Dental cones:**
  - A tablet form intended to be placed in the empty socket following a tooth extraction, for preventing the local multiplication of pathogenic bacteria associated with tooth extractions.
  - The cones may contain an antibiotic or antiseptic.
- **Pills:**
  - Pills are oral dosage forms which consist of spherical masses prepared from one or more medicaments incorporated with inert excipients.
  - Pills are now rarely used.

➢ **Liquid Forms:**

- **Solution:**
  - Oral solutions are clear Liquid preparations for oral use containing one or more active ingredients dissolved in a suitable vehicle.

✓ **Advantages:**

- Easier to swallow therefore easier for: children, old age, unconscious people.
- More quickly effective than tablets and capsules.
- Homogenous therefore give uniform dose than suspension or emulsion which need shaking.
- Dilute irritant action of some drugs (aspirin, KI, KBr) minimize adverse effects in the GIT like KCl.

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✕ **Disadvantages:**

- Bulky therefore difficult to transport and store.
- Unpleasant taste or odours are difficult to mask.
- Needs an accurate spoon to measure the dose.
- Less stable than solid dosage forms. major signs of instability: colour change, precipitation, microbial growth, chemical gas formation.

- Syrup:
  - It is a concentrated aqueous solution of a sugar, usually sucrose to which medicaments are added.
  - Flavored syrups are a convenient form of masking disagreeable tastes.
  - Examples of drugs administered by this route: e.g. Fevadol, Salbutamol, Adol & Coldex-D.

✓ **Advantages:**

- Ability to disguise bad taste of medication (sweet taste).
- Thick character of syrup has soothing effect on irritated tissues of throat.
- Its viscosity prevents bacterial growth.
- Contain little or no alcohol.
- Easy to adjust the dose for a child's weight.

✕ **Disadvantages:**

- Not suitable for diabetic patient.
- Dental caries.
- Recrystallization of sugar.

- Suspension:
  - Liquid preparations for oral use containing one or more active ingredients suspended in a suitable vehicle.
  - May show a sediment which is readily dispersed on shaking to give a uniform suspension which remains sufficiently stable to enable the correct dose to be delivered.

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- Examples of drugs administered by this route: e.g. Calpol, Balkatrin, Biomox & Calmoxe 156.
  - ✓ **Advantages:**
    - Suitable for non-soluble drug.
    - Higher rate of bioavailability, as order of bioavailabilty is:
      Solution > Suspensions > Capsules > Compressed tablets.
  - ✕ **Disadvantages:**
    - Cake formation.
    - Should be shaken before use.
    - Physical stability, sedimentation and compaction.
    - Bulky, handling require care.
    - Uniform drug delivery can not be achieved sometimes.

- Emulsion:
  - Oral emulsions are stabilized oil-in-water dispersions, either or both phases of which may contain dissolved solids either oil is dispersed in finely divided form in water or vice versa.

  - Examples of drugs administered by this route: e.g. Calcio 20
    - ✓ **Advantages:**
      - Unpalatable oil-soluble drugs can be administered in palatable form.
      - The aqueous phase is easily flavoured.
      - The oily sensation is easily removed.
      - The rate of absorption is increased.
      - It is possible to include two incompatible ingredients, one in each phase of the emulsion.
      - EMULSIONS are simple, have few Ingredients and are cheap.
      - Reaction medium is mostly water therefore it easily penetrates in the skin.

✕ **Disadvantages:**

- Preparation needs to be shaken well before use.
- A measuring device is needed for administration.
- A degree of technical accuracy is needed to measure a dose.
- Storage conditions may affect stability.
- Bulky, difficult to transport and prone to container breakages.
- Liable to microbial contamination which can lead to cracking..
- Improper formulation may lead to creaming and cracking.

- Elixir:
  - It is pleasantly flavored clear liquid oral preparation of potent or nauseous drugs.
  - The vehicle may contain a high proportion of ethanol or sucrose together with antimicrobial preservatives which confers the stability of the preparation.

✓ **Advantages:**

- Suitable for diabetic patient.
- Better able to maintain both water-soluble and alcohol-soluble components in solution
- Has stable characteristics
- Easily prepared by simple solution.
- Easy to swallow than tablets or capsule.
- It tastes good.
- Clear solution, no need to be shuffled again.

✕ **Disadvantages:**

- Less effective than syrups in masking taste of medicated substances.
- Contains alcohol, accentuates saline taste of bromides.
- Alcohol is not good for children.
- Because they contain volatile materials, it must be stored in a watertight screw-top jar and away from sources of ignition.

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- Linctuses:
  - Are viscous, liquid oral preparations that are usually prescribed for the relief of cough.
  - Contain a high proportion of syrup and glycerol which have a demulcent effect on the membranes of the throat.
  - The dose volume is small (5ml) and, to prolong the demulcent action, they should be taken undiluted.

    - ✓ **Advantages:**
      - High viscosity.
      - Specific for treating cough.
      - Long duration of effect.
    - ✕ **Disadvantages:**
      - Dis. Of solution.
      - Bulk, need measurement etc.

- Oral drops:
  - Oral drops are Liquid preparations for oral use that are intended to be administered in small volumes with the aid of a suitable measuring device. They may be solutions, suspensions or emulsions.
  - Examples of drugs administered by this route: e.g. Bronex, Emedrop, Amol & Adol
    - ✓ **Advantages:**
      - Are useful for potent drugs.
      - Are used for infants.
    - ✕ **Disadvantages:**
      - Less stable.

- Mouthwashes:
  - These are similar to gargles but are used for oral hygiene and to treat infections of the mouth.
  - Examples of drugs administered by this route: e.g. Slica Herb.

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✓ **Advantages:**

- Can boost your oral health.
- May prevent plaque from building up.
- Rinses with fluoride can help prevent cavities. Fluoride protects against tooth decay (cavities).
- Mouthwash can help you target plaque.
- Prevents dry mouth.

✕ **Disadvantages:**

- Some mouth rinses contain high levels of alcohol—ranging from 18 to 26 percent. This may produce aburning sensation in the cheeks, teeth, and gums.
- Mouthwash can be dangerous for children when ingested.
- Mouthwash can damage some parts of the mouth. Mouthwashes with high alcohol content can burn the delicate mucus membranes in the mouth.
- Mouthwash can stain and darken teeth.

- Gargles:
  - They are aqueous solutions used in the prevention or treatment of throat infections.
  - Usually they are prepared in a concentrated solution with directions for the patient to dilute with warm water before use.

✓ **Advantages:**

- Local effect.

✕ **Disadvantages:**

- Local irritation.
- Difficult to proper use.

❖ Topical Dosage Forms:

➢ Semi-solid Forms:

- Ointments:
  - Ointments are semi-solid, greasy preparations for application to the skin, rectum or nasal mucosa.
  - The base is usually anhydrous and immiscible with skin secretions.

- Ointments may be used as emollients or to apply suspended or dissolved medicaments to the skin, & they make barrier on skin to prevent water loss.
- Examples of drugs administered by this route: e.g. Tetracycline.

✓ **Advantages:**

- They are chemically more stable than liquid dosage forms.
- They facilitate application of the directly to the effected body part and avoid exposure of other parts to the drug.
- They are suitable for patients who find it difficult to take the drugs by parenteral and oral routes.
- They prolong the contact time between the drug and effected area.
- The bioavailability of drugs administered as ointments is more since it prevents passage through liver.

✕ **Disadvantages:**

- Not suitable for use on large area of skin.
- More greasy.
- Difficult to wash.
- Need massage.
- Not for use during day or face application.
- When application of an exact quantity of ointment to the affected area is required, it is difficult to ascertain the same.
- They are less stable than solid dosage forms.

- Creams:
  - Creams are semi-solid emulsions, that is mixtures of oil and water.
  - They are divided into **two types**:
    - **Oil-in-water (O/W) creams:** which are composed of small droplets of oil dispersed in a continuous aqueous phase.

Oil-in-water creams are more comfortable & cosmetically acceptable as they are less greasy and more easily washed off using water.

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- **Water-in-oil (W/O) creams:** which are composed of small droplets of water dispersed in a continuous oily phase.
  Water-in-oil creams are more difficult to handle but many drugs which are incorporated into creams are hydrophobic and will be released more readily from a water-in-oil cream than an oil-in-water cream.
  Water-in-oil creams are also more moisturizing as they provide an oily barrier which reduces water loss from the stratum corneum, the outer most layer of the skin.

- Examples of drugs administered by this route: e.g. Dermatin & Betasone.

✓ **Advantages:**

- Easy washing.
- Less greasy than ointment.
- Suitable for use during day and face application.
- It prevents dryness.

✕ **Disadvantages:**

- Need massage.
- Not suitable for use on large area of skin.
- It is less stable because it is composed of water, so bacterial growth can occur.

- Gels (Jellies):
  - Gels are semisolid system in which a liquid phase is constrained within a 3-D polymeric matrix (consisting of natural or synthetic gum) having a high degree of physical or chemical cross-linking.
  - They are used for medication, lubrication and some miscellaneous applications like carrier for spermicidal agents to be used intra vaginally.

✓ **Advantages:**

- Doesn't need massage.
- Rapid absorption.
- Easy washing.

✕ **Disadvantages:**

- They may cause skin allergy during application.

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- Pastes:
  - Pastes are basically ointments into which a high percentage of insoluble solid has been added.
  - The extraordinary amount of particulate matter stiffens the system.
  - Pastes are less penetrating and less macerating and less heating than ointment.
  - Pastes make particularly good protective barrier when placed on the skin, the solid they contain can absorb and thereby neutralize certain noxious chemicals before they ever reach the skin.
  - Like ointments, paste forms an unbroken relatively water-impermeable film unlike ointments the film is opaque and therefore can be used as an effective sun block accordingly.
  - There are **two types** of paste:
    - **Fatty pastes** (e.g: leaser's paste).
    - **Non greasy pastes** (e g: - bassorin paste).

    ✓ **Advantages:**
    - Create a barrier which doesn't melt at body temperature.
    - Sunblock manufacturing.
- Patches:
  - A drug delivery system that contains an adhesived backing and that permits its ingredients to diffuse from some portion of it (e.g., the backing itself, a reservoir, the adhesive, or some other component) into the body from the external site where it is applied.
  - Supports passage of drug through skin into systemic circulation.
- Plasters:
  - Plasters are solid or semisolid masses adhere to the skin when spread upon cotton felt line or muslin as a backing material and they are mainly used to:
    - Afford protection and mechanical support.
    - Furnish an occlusive and macerating action.
    - Bring medication into close contact with the surface of the skin.

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- Poultice:
  - It is soft, viscous, pasty preparation for external use. They are applied to skin while they are hot. Poultice must retain heat for a considerable time because they are intended to supply warmth to inflamed parts of body. E.g. Kaolin poultice (B.P.C.)
- Dusting powders:
  - These are free flowing very fine powders for external use.
  - Not for use on open wounds unless the powders are sterilized.

➢ **Liquid Forms:**

- Lotions:
  - These are fluid preparations (aqueous) for external application without friction – either dabbed on the skin or applied on a suitable dressing and covered with a waterproof dressing to reduce evaporation.
  - Examples of drugs administered by this route: e.g. Calamyl & Diprosalic.

✓ **Advantages:**
- No need for massage.
- Cooling of skin.
- It is anti-septic.
- Rapid evaporation.
- Cover large area.

✕ **Disadvantages:**
- It is uncomfortable (skin covered with powder).
- It is vulnerable to be lost when changing cloths.
- The user can't leave house.

- Pressurized dispensers (aerosol sprays):
  - Several different types of pharmaceutical product may be packaged in pressurized dispensers, known as aerosols.
  - Surface sprays produce droplets of 100 um diameter or greater.
  - May be used as surface disinfectants, wound or burn dressing, relieve irritation of bites.

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- Spray-on dusting powders are also available from pressurized containers.
  - ✓ **Advantages:**
    - Easily withdrawn of drug
    - Easy and convenient to apply.
    - Faster Onset of action.
    - No manual / direct contact with the medicament.
    - Avoid the first pass metabolism.
    - A specific amount of dose or drug can be removed.
    - No microorganism can enter.
    - Release the contents in Controlled and Uniformly.
    - Protect the photosensitive medicaments and oxygen sensitive material.
    - Provides efficacy of a drug.
    - Irritation can be reduced.
  - ✕ **Disadvantages:**
    - Costly.
    - Difficult disposal of empty aerosol containers.
    - Allergic in some cases.
    - Explosive.
    - Some formulation is difficult.
    - Sometimes propellants may cause toxic reactions.

- **Liniments:**
  - Liniments are fluid, semi-fluid or, occasionally, semi-solid preparations intended for application to the skin.
  - They may be alcoholic or oily solutions or emulsions.
  - Most are massaged into the skin (e.g. counter-irritant).
  - Liniments should not be applied to broken skin.
- **Collodion:**
  - Collodion is a solution of nitrocellulose in ether or acetone, sometimes with the addition of alcohols.
  - Its generic name is pyroxylin solution.

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- It is highly flammable.
- As the solvent evaporates, it dries to a celluloid-like film.
- Compound Wart Remover consists of acetic acid and salicylic acid in an acetone collodion base used in Treatment of warts by keratolysis.

- Paints:
  - Paints are liquids for application to the skin or mucous membranes.
  - Skin paints contain volatile solvent that evaporates quickly to leave a dry resinous film of medicament.
  - Throat paints are more viscous due to a high content of glycerol, designed to prolong contact of the medicament with the affected site.

❖ Rectal Dosage Forms:

➢ Semi-solid Forms:

- Suppository:
  - It is a small solid medicated mass, usually cone-shaped, that is inserted either into the rectum (rectal suppository), vagina (vaginal suppository or pessaries) where it melts at body temperature.
  - Examples of drugs administered by this route: e.g. Revanin Children.

✓ **Advantages:**

- Can exert local effect on rectal mucosa.
- Used to promote evacuation of bowel.
- Avoid any gastrointestinal irritation.
- Can be used in unconscious patients (e.g. during fitting).
- May be used in comatose patients or those with difficulty swallowing.
- Used in presence of nausea & vomiting.
- Can be used for systemic absorption of drugs and avoid first-pass metabolism.
- Avoids gastric juices: some drugs are destroyed or inactivated by the pH of the stomach or intestines.

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- Easy administration to infants & small children (often used when IV access is difficult).
- Post operative people who cannot be administered oral medication.
- Used both locally & systemically: locally used to relieve constipation, pain, irritation, itching & inflammation.
- Used in psychotic patients & patients prone to drug abuse.

✕ **Disadvantages:**

- The problem of patient acceptability.
- Suppositories are not suitable for patients suffering from diarrhea.
- In some cases the total amount of the drug must be given will be either too irritating or in greater amount than reasonably can be placed into suppository.
- Incomplete absorption may be obtained because suppository usually promotes evacuation of the bowel.
- Difficult to insert.
- Some require cool storage.

➢ **Liquid Forms:**

- Enema:
  - An enema is the procedure of introducing liquids into the rectum and colon via the anus.
  - **Types** of enema:
    - **Evacuant enema:** used as a bowel stimulant to treat constipation. E.g. soft soap enema & $MgSO_4$ enema.
      The volume of evacuant enemas may reach up to 2 liters.
      They should be warmed to body temperature before administration.
    - **Retention enema:** Their volume does not exceed 100 ml.
      No warming needed.
      May exert:
      - **Local effect:** e.g. a barium enema is used as a contrast substance in the radiological imaging of the bowel.

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- **Systemic effect:** e.g. the administration of substances into the blood stream. This may be done in situations where it is impossible to deliver a medication by mouth, such as antiemetics.
  e.g. nutrient enema which contains carbohydrates, vitamins & minerals.

- Examples of drugs administered by this route: e.g. Quality Disposable.

✓ **Advantages:**

- Generally quick acting.
- Local effect.
- Can administer large volume into rectum.

✕ **Disadvantages:**

- Unpleasant or inconvenient to use (usually given at night to minimize movement).
- Self-administration often is difficult if not impossible.
- It is uncomfortable.
- Needs a specialist.

❖ Vaginal Dosage Forms:

➢ Semi-solid Forms:

- Pessary (vaginal suppository):
  - Pessaries are solid medicated preparations designed for insertion into the vagina where they melt or dissolve.
  - There are **three types**:
    - **Moulded pessaries:** they are cone shaped and prepared in a similar way to moulded suppositories.
    - **Compressed pessaries:** made in a variety of shapes and are prepared by compression in a similar manner to oral tablets.
    - **Vaginal capsules:** are similar to soft gelatin oral Capsules differing only in size and shape.
  - Examples of drugs administered by this route: e.g. Monicure & Gynozol.

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- Douches:
  - Are squeezable bottles design to introduce stream of water to body cavity like vagina, used by dissolving a medication in water then putting them in douches and administered.
  - Used for clearing and washing of the vagina.

❖ Parenteral Dosage Forms:

- Ampule:
  - Is a small sealed vial which is used to contain and preserve a sample, usually a solid or liquid. Ampoules are commonly made of glass, although plastic ampoules do exist.
- Vial:
  - Is a small glass or plastic vessel or bottle, often used to store medication as liquids, powders or capsules.
- Infusion:
  - Is a dilute solution of the readily soluble constituents of crude drugs from the soft parts of plants.

- An injection:
  - An injection is an infusion method of putting liquid into the body, usually with a hollow needle and a syringe which is pierced through the skin to a sufficient depth for the material to be forced into the body.
  - There are several **methods of injection**, including:
    - **An intravenous injection:** It is a liquid administered directly into the bloodstream via a vein. It is advantageous when a rapid onset of action is needed.
    - **Intramuscular injection:** It is the injection of a substance directly into a muscle. Many vaccines are administered intramuscularly. Depending on the chemical properties of the drug, the medication may either be absorbed fairly quickly or more gradually. Intramuscular injections are often given in the deltoid, vastus lateralis, ventrogluteal and dorsogluteal muscles.

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Injection fibrosis is a complication that may occur if the injections are delivered with great frequency or with improper technique.

- **Subcutaneous injection:** Subcutaneous injections are given by injecting a fluid into the subcutis, the layer of skin directly below the dermis and epidermis.

  Subcutaneous injections are highly effective in administering vaccines and such medications as insulin.

❖ Inhaled Dosage Forms:

- Inhaler:
  - Inhalers are solutions, suspensions or emulsion of drugs in a mixture of inert propellants held under pressure in an aerosol dispenser.
  - Release of a dose of the medicament in the form of droplets of 50 um diameter or less from the container through a spring-loaded valve incorporating a metering device. The patient then inhales the released drug through a mouthpiece.

  - In some types, the valve is actuated by finger pressure, in other types the valve is actuated by the patient breathing in through the mouthpiece.
  - It is commonly used to treat asthma and other respiratory problems.
  - Examples of drugs administered by this route: e.g. Ventolin & Foracort-200.

  ✓ **Advantages:**
  - Rapid onset of action and absorption.
  - Used for asthma.
  - Easy holding.
  - Systemic effect.
  - Accurate dose.

  ✕ **Disadvantages:**
  - Local irritation (toxic).
  - Expensive.
  - Explosive.
  - Not preferred to be used for long time.

- Nebulizer or (atomizer):
  - A nebulizer is a device used to administer medication to people in forms of a liquid mist to the airways.
  - It is commonly used in treating asthma, and other respiratory diseases.
  - It pumps air or oxygen through a liquid medicine to turn it into a vapor, which is then inhaled by the patient.

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- As a general rule, doctors generally prefer to prescribe inhalers for their patients, because:
  - These are cheaper
  - More portable
  - Carry less risk of side effects.

    * Nebulizers, for that reason, are usually reserved only for serious cases of respiratory disease, or severe attacks.

❖ Ophthalmic Dosage Forms:

- Eye drops:
  - Eye drops are saline-containing drops used as a vehicle to administer medication in the eye.
  - Depending on the condition being treated, they may contain steroids, antihistamines or topical anesthetics.
  - Eye drops sometimes do not have medications in them and are only lubricating and tear-replacing solutions.
  - Examples of drugs administered by this route: e.g. Alcon Mydriacyl & Apicarpin.

✓ **Advantages:**
- Local effect.
- It can be used as a lubricant.

✕ **Disadvantages:**
- Local irritation.
- Weak stability.
- Needs to be careful during using
- They must be sterilized, of high viscosity and pH= 7.2 - 7.4

- Ophthalmic ointment & gel:
  - These are sterile semi-solid Preparations intended for application to the conjunctiva or eyelid margin.

    ✓ **Advantages:**
    - Longer contact time and greater storage stability.
    - Flexibility in drug choice.
    - Improved drug stability.

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✕ **Disadvantages:**

- Sticking of eyes lids.
- Blurred vision.
- Poor patient compliance
- Interfere with the attachment of new corneal epithelial cells to their normal base.
- Matting of eyelids.

❖ Otic Dosage Forms:

- Ear drops:
  - Ear drops are solutions, suspensions or emulsions of drugs that are instilled into the ear with a dropper.
  - It is used to treat or prevent ear infections, especially infections of the outer ear and ear canal.
  - Examples of drugs administered by this route: e.g. Otocalm.

✓ **Advantages:**

- Presence of oil.
- High viscosity (by cellulose).

✕ **Disadvantages:**

- Losing of drug from ear.
- Not easy to self administeration.

❖ Nasal Dosage Forms:

- Nasal Drops and Sprays:
  - Drugs in solution may be instilled into the nose from a dropper or from a plastic squeeze bottle.
  - The drug may have a local effect, e.g. antihistamine, decongestant.
  - Alternatively the drug may be absorbed through the nasal mucosa to exert a systemic effect.
  - The use of oily nasal drops should be avoided because of possible damage to the cilia of the nasal mucosa.
  - Examples of drugs administered by this route: e.g. Rhinex, Rinomist & Flixonase.

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✓ **Advantages:**
- Local effect.

✕ **Disadvantages:**
- Local irritation.

❖ **Intermediate products used in compounding:**

- Extracts:
  These are concentrated preparations containing the active principals of vegetable or animal drugs which have been extracted with suitable solvents and concentrated to form liquid, soft or dry extract.
- Glycerins:
  These are solutions of medicaments in glycerol with or without the addition of water.
- Infusions:
  These are dilute solutions containing the readily soluble constituents of crude drugs and prepared by diluting 1 part of concentrated infusion with 10 parts of water. Concentrated infusions are prepared by cold extraction of crude drugs with 25% ethanol.
- Oxymels:
  These are preparations in which the vehicle is a mixture of acetic acid and honey.
- Spirits:
  They are alcoholic or aqueous alcoholic solutions of volatile substances used as flavouring agents.
- Tinctures:
  These are alcoholic preparations containing the active principals of vegetable drugs. They are relatively weak compared to extracts.
- Aromatic waters:
  These are aqueous solutions, usually saturated of volatile oils or other volatile substances. Used as flavoring agents.

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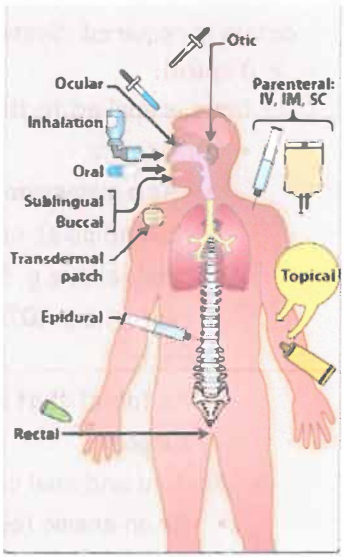
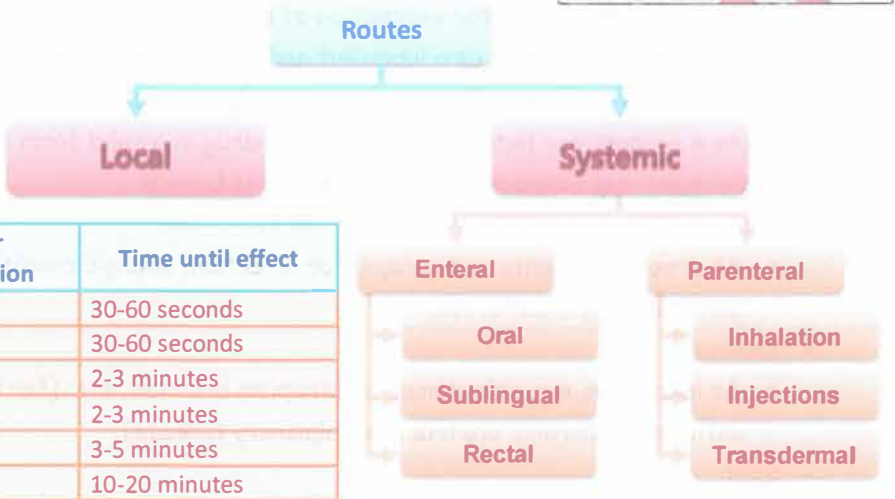
Routes of Drug Administration

Most of the drugs can be administered by different routes. Drug and patient-related factors determine the selection of routes for drug administration. The factors are:

- Characteristics of the drug.
- Emergency/routine use.
- Site of action of the drug—local or systemic.
- Condition of the patient (unconscious, vomiting, diarrhoea).
- Age of the patient.
- Effect of gastric pH, digestive enzymes and first-pass metabolism.
- Patient's/doctor's choice (sometimes).





Route for administration	Time until effect
Intravenous	30-60 seconds
Intraosseous	30-60 seconds
Endotracheal	2-3 minutes
Inhalation	2-3 minutes
Sublingual	3-5 minutes
Intramuscular	10-20 minutes
Subcutaneous	15-30 minutes
Rectal	5-30 minutes
Ingestion	30-90 minutes
Transdermal (topical)	variable (minutes to hours)

❖ Local Routes:

It is the simplest mode of administration of a drug at the site where the desired action is required. Systemic side effects are minimal.

➢ Topical:

Drug is applied to the skin or mucous membrane at various sites for local action.

- Oral cavity:
  - As a suspension, e.g. nystatin; as a troche, e.g. clotrimazole (for oral candidiasis); as a cream, e.g. acyclovir (for herpes labialis); as ointment and jelly, e.g. 5% lignocaine hydrochloride (for topical anaesthesia); as a spray, e.g. 10% lignocaine hydrochloride (for topical anaesthesia).
- GI tract:
  - As tablet that is not absorbed, e.g. neomycin (for sterilization of gut before surgery).
- Rectum and anal canal:
  - As an enema (administration of drug into the rectum in liquid form):
    - Evacuant enema (for evacuation of bowel): For example, soap water enema—soap acts as a lubricant and water stimulates the rectum.
    - Retention enema: For example, methylprednisolone in ulcerative colitis.
  - As a suppository (administration of the drug in a solid form into the rectum), e.g. bisacodyl— for evacuation of bowels.
- Eye, ear and nose:
  - As drops, ointments and sprays (for infection, allergic conditions, etc.), e.g. gentamicin eye/ear drops.
- Bronchi:
  - As inhalation, e.g. salbutamol, ipratropium bromide, etc. (for bronchial asthma and chronic obstructive pulmonary disease).
- Skin:
  - As ointment, cream, lotion or powder, e.g. clotrimazole (antifungal) for cutaneous candidiasis.

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- **Intra-arterial route:**
  This route is rarely employed. It is mainly used during diagnostic studies such as coronary angiography and for the administration of some anticancer drugs, e.g. for treatment of malignancy involving limbs.
- **Administration of the drug into some deep tissues** by injection, e.g. administration of triamcinolone directly into the joint space in rheumatoid arthritis.

Systemic Routes:

Drugs administered by this route enter blood and produce systemic effects

Enteral Routes:

It includes oral, sublingual and rectal routes.

- **Oral Route:**
  It is the most common and acceptable route for drug administration. Dosage forms are tablet, capsule, syrup, mixture, etc., e.g., paracetamol tablet for fever, omeprazole capsule for peptic ulcer are given orally.
  - Advantages:
    - Safer.
    - Cheaper.
    - Painless.
    - Convenient for repeated and prolonged use.
    - Can be self-administered..
  - Disadvantages:
    - Not suitable for emergency as onset of action of orally administered drugs is slow.
    - It is not suitable for/in:
      - Unpalatable and highly irritant drugs.
      - Unabsorbable drugs (e.g. aminoglycosides).
      - Drugs that are destroyed by digestive juices (e.g. insulin).
      - Drugs with extensive first-pass metabolism (e.g. lignocaine).
      - Unconscious patients.
      - Uncooperative and unreliable patients.
      - Patients with severe vomiting and diarrhoea.

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➢ **Sublingual Route:**

The preparation is kept under the tongue. The drug is absorbed through the buccal mucous membrane and enters the systemic circulation directly, e.g. nitroglycerin for acute anginal attack and buprenorphine for myocardial infarction.

- Advantages:
  - Quick onset of action.
  - Action can be terminated by spitting out the tablet.
  - Bypasses first-pass metabolism.
  - Self-administration is possible.
- Disadvantages:
  - It is not suitable for:
    - Irritant and lipid-insoluble drugs.
    - Drugs with bad smell and taste.

➢ **Rectal Route:**

Drugs can be given in the form of solid or liquid.

- Suppository:
  - It can be used for local (topical) effect as well as systemic effect, e.g. indomethacin for rheumatoid arthritis.
- Enema:
  - Retention enema can be used for local effect as well as systemic effect. The drug is absorbed through rectal mucous membrane and produces systemic effect, e.g. diazepam for status epilepticus in children.

❖ Parenteral Routes:

Routes of administration other than enteral route are called parenteral routes.

- Advantages:
  - Onset of action of drugs is faster; hence it is suitable for emergency.
  - Useful in:
    - Unconscious patient.
    - Uncooperative and unreliable patients.
    - Patients with vomiting and diarrhoea.

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- It is suitable for:
  - Irritant drugs.
  - Drugs with high first-pass metabolism.
  - Drugs not absorbed orally.
  - Drugs destroyed by digestive juices.
- Disadvantages:
  - Require aseptic conditions.
  - Preparations should be sterile and is expensive.
  - Requires invasive techniques that are painful.
  - Cannot be usually self-administered.
  - Can cause local tissue injury to nerves, vessels, etc.

➢ **Inhalation:**

Volatile liquids and gases are given by inhalation for systemic effects, e.g. general anaesthetics.

- Advantages:
  - Quick onset of action.
  - Dose required is very less, so systemic toxicity is minimized.
  - Amount of drug administered can be regulated.
- Disadvantages:
  - Local irritation may cause increased respiratory secretions and bronchospasm.

❖ **Injections (Fig. 1.1):**

➢ **Intradermal route:**

The drug is injected into the layers of the skin, e.g. Bacillus Calmette-Guérin (BCG) vaccination and drug sensitivity tests. It is painful and only a small amount of the drug can be administered.

➢ **Subcutaneous (s.c.) route:**

The drug is injected into the subcutaneous tissues of the thigh, abdomen and arm, e.g. adrenaline, insulin, etc.

- Advantages:
  - Self-administration is possible (e.g. insulin).
  - Depot preparations can be inserted into the subcutaneous tissue, e.g. norplant for contraception.

- Disadvantages:
  - It is suitable only for nonirritant drugs.
  - Drug absorption is slow; hence it is not suitable for emergency.

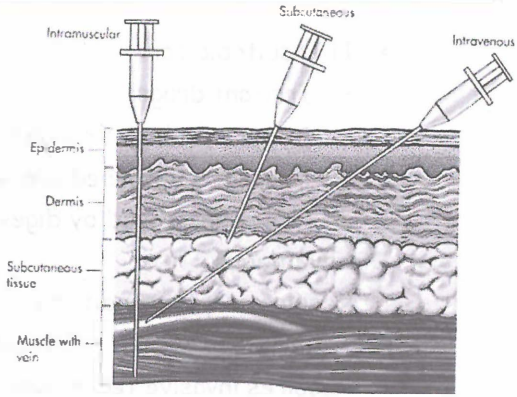

Fig. 1.1 Injectable routes of drug administration.

➢ **Intramuscular (i.m.) route:**

Drugs are injected into large muscles such as deltoid, gluteus maximus and vastus lateralis, e.g. paracetamol, diclofenac, etc. A volume of 5–10 mL can be given at a time.

- Advantages:
  - Absorption is more rapid as compared to oral route.
  - Mild irritants, depot injections, soluble substances and suspensions can be given by this route.
- Disadvantages:
  - Aseptic conditions are needed.
  - Intramuscular injections are painful and may cause abscess.
  - Self-administration is not possible.
  - There may be injury to the nerves.

➢ **Intravenous (i.v.) route:**

Drugs are injected directly into the blood stream through a vein. Drugs are administered as:

1- **Bolus:** Single, relatively large dose of a drug injected rapidly or slowly as a single unit into a vein. For example, i.v. ranitidine in bleeding peptic ulcer.

2- **Slow intravenous injection:** For example, i.v. morphine in myocardial infarction.

3- **Intravenous infusion:** For example, dopamine infusion in cardiogenic shock; mannitol infusion in cerebral oedema; fluids infused intravenously in dehydration.

- Advantages:
  - Bioavailability is 100%.
  - Quick onset of action; therefore, it is the route of choice in emergency, e.g. intravenous diazepam to control convulsions in status epilepticus.

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- Large volume of fluid can be administered, e.g. intravenous fluids in patients with severe dehydration.
- Highly irritant drugs, e.g. anticancer drugs can be given because they get diluted in blood.
- Hypertonic solution can be infused by intravenous route, e.g. 20% mannitol in cerebral oedema.
- By i.v. infusion, a constant plasma level of the drug can be maintained, e.g. dopamine infusion in cardiogenic shock.

- Disadvantages:
  - Once the drug is injected, its action cannot be halted.
  - Local irritation may cause phlebitis.
  - Self-medication is not possible.
  - Strict aseptic conditions are needed.
  - Extravasation of some drugs can cause injury, necrosis and sloughing of tissues.
  - Depot preparations cannot be given by i.v. route.
- Precautions:
  - Drug should usually be injected slowly.
  - Before injecting, make sure that the tip of the needle is in the vein.

➢ **Intrathecal route:**

Drug is injected into the subarachnoid space (spinal anaesthetics, e.g. lignocaine; antibiotics, e.g. amphotericin B, etc.).

➢ **Intra-articular route:**

Drug is injected directly into the joint space, e.g. hydrocortisone injection for rheumatoid arthritis. Strict aseptic precautions should be taken. Repeated administration may cause damage to the articular cartilage.

➢ **Transdermal route:**

The drug is administered in the form of a patch or ointment that delivers the drug into the circulation for systemic effect (Fig. 1.2).

For example, scopolamine patch for sialorrhoea and motion sickness, nitroglycerin patch/ointment for angina, oestrogen patch for hormone replacement therapy (HRT).

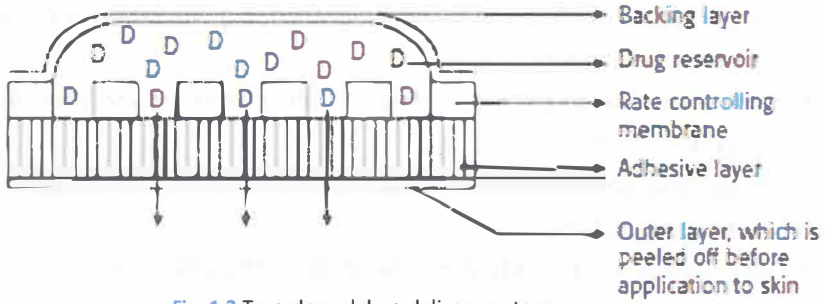

Fig. 1.2 Transdermal drug-delivery system.

- Advantages:
  - Self-administration is possible.
  - Patient compliance is better.
  - Duration of action is prolonged.
  - Systemic side effects are reduced.
  - Provides a constant plasma concentration of the drug.
- Disadvantages:
  - Expensive.
  - Local irritation may cause dermatitis and itching.
  - Patch may fall-off unnoticed.

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Route of Administration	Absorption Pattern	ADVANTAGES	DISADVANTAGES
Oral	• Variable; affected by many factors	• Safest and most common, convenient, and economical route of administration	• Limited absorption of some drugs • Food may affect absorption • Patient compliance is necessary • Drugs may be metabolized before systemic absorption
Intravenous	• Absorption not required	• Can have immediate effects • Ideal if dosed in large volumes • Suitable for irritating substances and complex mixtures • Valuable in emergency situations • Dosage titration permissible • Ideal for high molecular weight proteins and peptide drugs	• Unsuitable for oily substances • Bolus injection may result in adverse effects • Most substances must be slowly injected • Strict aseptic techniques needed
Subcutaneous	• Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained	• Suitable for slow-release drugs • Ideal for some poorly soluble suspensions	• Pain or necrosis if drug is irritating • Unsuitable for drugs administered in large volumes
Intramuscular	• Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained	• Suitable if drug volume is moderate • Suitable for oily vehicles and certain irritating substances • Preferable to intravenous if patient must self-administer	• Affects certain lab tests (creatine kinase) • Can be painful • Can cause intramuscular hemorrhage (precluded during anticoagulation therapy)
Transdermal (patch)	• Slow and sustained	• Bypasses the first-pass effect • Convenient and painless • Ideal for drugs that are lipophilic and have poor oral bioavailability • Ideal for drugs that are quickly eliminated from the body	• Some patients are allergic to patches, which can cause irritation • Drug must be highly lipophilic • May cause delayed delivery of drug to pharmacological site of action • Limited to drugs that can be taken in small daily doses
Rectal	• Erratic and variable	• Partially bypasses first-pass effect • Bypasses destruction by stomach acid • Ideal if drug causes vomiting • Ideal in patients who are vomiting, or comatose	• Drugs may irritate the rectal mucosa • Not a well-accepted route
Inhalation	• Systemic absorption may occur; this is not always desirable	• Absorption is rapid; can have immediate effects • Ideal for gases • Effective for patients with respiratory problems • Dose can be titrated • Localized effect to target lungs: lower doses used compared to that with oral or parenteral administration • Fewer systemic side effects	• Most addictive route (drug can enter the brain quickly) • Patient may have difficulty regulating dose • Some patients may have difficulty using inhalers
Sublingual	• Depends on the drug: Few drugs (for example, nitroglycerin) have rapid, direct systemic absorption Most drugs erratically or incompletely absorbed	• Bypasses first-pass effect • Bypasses destruction by stomach acid • Drug stability maintained because the pH of saliva relatively neutral • May cause immediate pharmacological effects	• Limited to certain types of drugs • Limited to drugs that can be taken in small doses • May lose part of the drug dose if swallowed

STUDY OF ABSORPTION AND EXCRETION OF DRUGS IN MAN

❖ OBJECTIVES:

At the end of the practical class the student shall be able to:

- Quantitatively estimate the levels of aspirin and iodide excreted in the urine & saliva respectively.
- Understand the importance of timing sample collection in relation to drug intake when estimating drug levels
- Explain how alteration in the pH of urine can increase or decrease the amount of drug eliminated in urine.

A. Potassium iodide:

➢ Drugs & solutions:

- Potassium iodide 0.3 g capsules
- 0.1% solution of KI serially diluted to 0.03%, 0.01% and 0.003%
- Sulphuric acid 3% solution
- Hydrogen peroxide
- Starch solution 0.5% in distilled water.

➢ **Apparatus:** Droppers, glass rods and porcelain tile.

❖ PROCEDURE:

One student will swallow a capsule (0.3g) of Potassium iodide and will examine the saliva every fifteen minutes.

❖ Preparation of standard:

To 2 drops each of the above standard KI solutions add 2 drops of sulphuric acid, one drop of hydrogen peroxide and one drop of starch solution. The development of a blue colour denotes a positive test the intensity of which indicates the concentration of KI. Prepare fresh standards for each subsequent test.

❖ Testing the samples of saliva:

The procedure is the same as that for the standard except that the standard solution is replaced by 2 drops of saliva. The approximate values are obtained by direct matching with the standards.

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B. Aspirin:

➢ Drugs & solutions:

- Aspirin tablet 300 mg.
- Standard aspirin solutions 0.1%, 0.05%, 0.01%, 0.005%
- Ferric chloride solution 2%

➢ **Apparatus:** Test tubes, Droppers.

❖ PROCEDURE:

One student takes a tablet of aspirin and will examine his urine at 20 mins. intervals for the presence of salicylate as per the following procedure.

❖ Preparation of standard:

To 3 ml of standard aspirin solution in a test tube add 2 drops of ferric chloride. A purple colour denotes the presence of salicylates.

❖ Testing the samples of urine:

To 3 ml of urine add ferric chloride solution slowly drop-wise (not more than 5 drops) along the walls of the test-tube until a purple colour develops. The approximate concentration of salicylate in the urine is obtained by direct matching with the standards.

Hints

- **The standards are usually prepared in water which will account for the difference in colour seen with the control and test (urine) samples. Yet, it is possible to match at the moment the solution (ferric chloride) makes contact with the urine. Hold the test tubes against the light for a better match.**
- **Results are tabulated and plotted in a graph paper (X axis time, Y axis concentration) to show the rate of excretion consequent to absorption. Insist on the observations being drawn on a graph paper.**

Drugs Dose Calculation

❖ Why we need to modify drug dosages?

✓ The nature of the systemic effects of drugs depend on the amount of drug, route of its administration and amount of its absorption and the following other factors:

*Note: The study of the dose is known as **Posology**.

1. Age:

- The dose is the amount of a drug which gives the desired therapeutic effect in average number i.e., 50% of patients (ED50) - The minimal dose is the smallest amount which has therapeutic effect in 50% patient and maximal dose is the largest tolerated does in average patients without toxic symptoms.
- The therapeutic dose lies between these two doses. The median lethal dote (LD50) is the amount of drug which is fatal in the 50% of experimental animals.
- The Therapeutic Index (TI) is found by dividing the (LD50) by the therapeutic dose (ED50).
- The British Pharmacopoeia gives average dose for the adult person between eighteen to sixty years of age.
- The children below 18 and persons above 60 should be given a dose below the adult dose to avoid adverse effect .There are a few formulae for calculation of dose of the children under 12 years.

$$\textbf{Young's Rule} = (\text{Age} \times \text{Adult dose}) / \text{Age} + 12$$

➢ **Example:**

Thus the dose of sodium bicarbonate for a child of 6 years = Adult dose of sodium bicarbonate is 1—4 Gram. Hence, the required dose will be

= 6 / (6+12) × 1 Gram = 1/3 Gram i.e. 1/3 to 1 × 1/3

- The dose required for the age between 12 to 16 years will be from 1/2 to 2/3 of the adult dose.
- The children can tolerate iron, belladonna, and chloral preparations relatively better than adult but they cannot tolerate opium and morphine preparations except in very small doses.

- The dose for infant can be calculated from their body surface and must not be calculated from the above formulae.

2. Weight:

- Most important factor, due to the body consider one compartment and as distribution compartment per each kilogram (Skeletal muscle is more important). And we have to know weight as well as how fat or lean the person is (% body fat)
- Drug achieves a higher concentration in smaller people given the same dosage (will produce a more intense effect)
- The "body surface area" calculation is better than body weight because it takes into account

Clark's Rule = (Weight of the child in Kilograms / 70) × Adult dose

3. Sex (Gender):

- Women usually, require a relatively smaller dose than man. The main reasons are the difference in the musculature structure (in Women there are more fat) and the monthly hormonal period.
- Drugs should be avoided as far as possible during pregnancy and lactation to prevent harmful effect on the fetus and the baby.

4. Time and route of administration:

- The action of drugs taken by mouth is greatly modified due to the presence or absence of food, in the stomach and intestine. The irritant drugs, like iron is better tolerated and absorbed when given after food. Adrenaline, Insulin, etc. should be given by Injection because they are destroyed by the digestive enzymes when given by mouth. Magnesium sulphate acts as purgative when given by mouth but acts as sedative when given by I.V. Sleeping pills acts better when given at bed time than during day time.

5. Tolerance & Addiction:

- Body has the capacity to handle certain drugs even when given repeatedly. As a result, their doses should be gradually increased to keep the action constant. This condition is called tolerance. Morphine, alcohol etc. . . show remarkable degree of tolerance in man. When taken for some time these

drugs not only show tolerance but also produce a mental and physical condition of intense urge to continue to take them. This is called addiction. If the drug is stopped the addicted people show withdrawal sickness and may even die.

6. Intolerance or Susceptibility:

- In this condition, some patients may develop the usual symptoms of overdose even when a therapeutic dose is given to them. In other words, its means a greater response than normal expected response to the ordinary dose.

7. Idiosyncrasy:

- This is an inherent peculiarity of the persons in responding to certain drugs in a way completely abnormal from the usual actions of that drug. Thus morphine may produce excitation instead of sedation. This reaction occurs usually from the very first dose of the drug. Some of these actions have been found to be due to genetic abnormality.

8. Drug allergy or Hypersensitivity:

- In this condition, the abnormal reaction occurs usually from the second or sub-sequent doses. The first dose (antigen) generally stimulates the body to produce some reactive substance (antibody), which sensitizes the tissues of the body. When a second dose of that drug is given the reaction {antigen—antibody reaction} occurs in the tissue called allergic reaction. The reactions may be immediate (anaphylactic) or a delayed one (hypersensitivity). The anaphylactic reactions are → fall of blood pressure, shock, collapse, bronchospasm, cyanosis and even death. The hypersensitivity reactions are → urticaria, skin rash, asthma, drug fever, dermatitis, hepatitis, hay fever etc. Antihistaminics, adrenaline and cortisone preparations are used to treat these reactions.

9. Synergism or Potentiation:

- When two similar drugs but not having action on the same site or do not cause same quality of action; are combined together, then one may enhance the response of the other. In that case, the combined effect of the two will produce response which is far greater than that of the either drug given alone in

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much larger dose and also greater than that could be expected from simple addition of their individual effects. This type of synergism is particularly found in anti-biotic combinations, such as penicillin and streptomycin, cloxacillin and penicillin and sulphonamide and trimethoprim. Adrenaline and cocaine and Mersalyl and ammonium chloride combinations show the other examples of potentiation.

10. Antagonism:

- The combined effect of the two drugs may be less than that of the effect of their individual dose, as one may oppose the action of the other. This condition is called antagonism. The important examples are the acetylcholine to atropine, histamine to antihistamine, morphine to nalorphine etc. This phenomenon of drug antagonism is utilized in the treatment of poisoning or overdose of the drugs by giving the appropriate antagonist called antidote. Nalorphine & Naloxone are the antidotes in morphine poisoning.

11. Pathological Condition:

- Pathological conditions of the body also modify the drug action. Digitalis glyco-sides improve the cardiac functions and cause diuresis only in the patient with congestive heart failure. Aspirin and other antipyretic reduce body temperat-ure only when there is fever.

12. Genetic factor:

- It also affects drug action due to genetic differences among the races and certain persons in the same population. Isoniazid may be acetylated either rapidly or slowly according to genetic difference in the person. In American black and white population 50% are rapid and 50% are slow acetylates and in Latin Americans 35% slow acetylates and hence more toxicity in them. Primaquine causes hemolytic anemia in those persons whose R.B.C, lacks the enzyme glucose 6phosphate dehydrogenase.

13. Cumulative action:

- Some drugs are excreted so slowly from the body such that therapeutic dose taken in 24 hours is not fully excreted by that time and if their daily administ-eration is continued even in therapeutic doses for some time, the drug concent-ration in the body is gradually increased and suddenly the toxic

symptoms develop. Emetine and glycosides of digitalis are important examples to produce this phenomenon.

14. Drug Plasma half-life:

- The falling of plasma concentration of a drug to its half of the initial level takes a constant or fixed time called half-life. Longer the half-life; the drug requires less frequent administration.

Youngs Formula

$$\text{Dose} = \{\text{Age} / (\text{age} + 12)\} \times \text{adult dose}$$

Clarks Formula

$$\text{Dose} = (\text{Weight in Kg} / 70) \times \text{adult dose}$$

❖ Summary:

1- **Age:** the dose should be decreased at age extremities (geriatrics, infant and children).
2- **Weight:** as distribution compartment per each kilogram (Skeletal muscle is more important).
3- **Gender (sex):**
   - Males: more muscular building (Skeletal) and Androgens (HE inducers) = larger doses.
   - Females: More bulky fat and estrogens (HE inhibitors) = smaller doses.
4- **Accumulation:** e.g.: digoxin.
5- **Route of Administration:** because the (bioavailability) I.V > Inhalation > I.M > S.C > Oral > Skin(topical) (rectal and SL)
6- **Pathological condition:** the drug exerts therapeutic effect only in the presence of disease. (Aspirin & fever – Digoxin & CHF)
7- **Intolerance or hypersensitivity:** Higher response to smaller doses.
8- **Tolerance:** the body response decrease to the usual dose.
9- **Idiosyncrasy:**
10- **Drug Interaction.**
11- **Metabolism:** Diet, Race, Species, health state…etc.

Methods of dose adjustment

❖ The patients who require dose modification:

- ✓ Patients who administrate drug with narrow therapeutic index T.I. eg. Theophylline.
- ✓ Patients with renal problems eg. Gentamycin
- ✓ Patients with high risk of drug toxicity eg. Aminoglycoside, antiarrhythmias, digoxin.
- ✓ Children and overweight patients.

❖ Methods of dose adjustment:

A) In Adults:

- **According to weight of the patient:**

  Loading dose, maintenance dose are calculated as follows:

  Dose = dose in (gm, mg, µg) × body weight in Kg

- **According to body surface area (BSA)**

  Accurate adult dose = (BSA of adult m^2 / 1.73 m^2) × adult dose

- **According to creatinine clearance (CrCl)**

  For male:

  CrCl = {(140 – age) (body weight or LBM)} / (72 × SCC) ml/min

  For female:

  CrCl of male × 0.85 ⟹

  Patient dose = (normal dose × patient CrCl) / normal CrCl 125 ml/min

Example:

Determine the LD, MD, of gentamycin for a 76-year-old male patient weighing 86 Kg. with height of 183 cm and having SCC of 2.4 mg/dl. The physician desires LD of 1.5 mg/Kg of LBM and DM of 1 mg/Kg of LBM to be administrated every 8 hours.

Solution:

Height → 183 - 152.5 = 30.5 cm --convert to inch--→ 30.5/2.54 = 12 inch

LBM = 50 + 2.3 × 12 = 77.6 Kg

For normal patient

LD = 1.5 mg × 77.6 Kg = 116 mg

MD = 1 mg × 77.6 Kg = 77.6 mg every 8 hours

For uremic patient

CrCl = {(140 – age) × LBM} / (72 × SCC) = {(140 – 76) × 77.6 Kg} / (72 × 2.4) = 28.7 ml/min

LD = (normal dose × patient CrCl) / 125 ml/min

= (116 mg × 28.7 ml/min) / 125 ml/min = 26.6 mg initial

MD = (77.6 mg × 28.7 ml/min) / 125 ml/min = 17.8 mg every 8 hours

B) In Children:

- **Young's rules:**

Child dose = {(age) / (age + 12)} × adult dose

- **Body surface area (BSA):**

Child dose = {child BSA m^2 / 1.73 m^2} × adult dose

- **Clark's rule:**

Child dose = {weight in Kg / 70} × adult dose

❖ Lean body mass (LBM) is used:

- ✓ In obese patients
- ✓ With aminoglycoside
- ✓ With digoxin

- **LBM can be calculated as follows:**

For male:

LBM = 50 Kg + 2.3 Kg for each inch of patient height over 5 feet

For females:

LBM = 45.5 Kg + 2.3 Kg for each inch in height over 5 feet

➢ **Notes:**

1 feet = 12 inch = 30.5 cm

1 inch = 2.54 cm

Example 1:

Calculate LBM for female patient weighing 60 Kg and measuring 160 cm in height.

Solution:

Height in feet = 160 / 30.5 = 5.24

5 ↓ feet, .24 ↘ inch ≈ 3

LBM = 45.5 Kg + (2.3 Kg × 3) = 52.4 Kg

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5 feet = 152.5 cm

→ 160 - 152.5 = 7.5 → 7.5 / 2.54 = 2.95 inch ≈ 3 inch

Example 2:

Determine the maintenance dose of digoxin for a 70-year-old male patient weighing 83 Kg with height of 180 cm. the physician desires the MD of 7 µg/Kg (0.07 mg) daily.

Solution:

MD = dose in µg/Kg × LBM

LBM = 50 Kg + (2.3 × each inch over 5 feet)

LBM → 5 feet = 152.5 → 180 – 152.5 = 27.5

27.5 / 2.54 = 11 inch

→ LBM = 50 + (2.3 × 11) = 75.3 Kg

MD = 7 × 75.3 = 527 µg daily

0.07 × 75.3 = 5.27 mg daily

Rational Prescribing Practices

❖ Who Are "Licensed Prescribers"?

✓ Prescribing privileges are controlled by the state licensing boards, Delegated powers by the state legislatures.

❖ Professions with prescribing privileges:

- Physician
- Dentist
- Podiatrist
- Veterinarian
- Optometrist
- Nurse Practitioner or Midwives
- Physician's assistants
- Pharmacists

➢ As Dentists

- We commonly prescribe antibiotics and analgesics. How often are we aware why we prescribe a particular antibiotic or pain-killer?
- How much are we contributing to the problem of antibiotic resistance?
- Have you ever asked yourself whether your children be able to fight their infections in the future with so many resistant bacteria around?
- Too many commercials (companies).Too many drugs. Many Dosage forms. Too many generics for each drug.

❖ What is Rational Use of Medicines?

✓ Rational use of drugs requires that patients receive medications:
Appropriate to their clinical needs. In doses that meet their own requirement, For an adequate period of time, And at lowest cost to them and their community (WHO 1985).

✓ In other words we should ensure that there is: **Appropriate indication.**
The decision to prescribe drug(s) is entirely based on medical rationale and that drug therapy is an effective and safe treatment.

✓ We should ensure that there is: **Appropriate drug.**
The selection of drugs is based on:

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- Efficacy.
- Safety.
- Suitability.
- Cost considerations.
- Storage Condition.

✓ We should ensure that there is: **Appropriate patient.**

- No contra-indications exist
- The adverse reactions is minimal,
- The drug is acceptable to the patient.

✓ We should ensure that there is: **Appropriate information.**

Regarding his or her condition and the medication(s) that are prescribed.

Patients should be provided with

- Relevant,
- Accurate,
- Important
- Clear information

✓ We should ensure that there is: **Appropriate monitoring.**

The anticipated and unexpected effects of medications should be appropriately monitored.

** Common Problems: The number of drugs per prescription is often more than needed, with an average of 2.4 up to 10 drugs, while generally one or two drugs should be sufficient.

❖ Rational drug use (From WHO Guide to Good Prescribing):

- **Step 1:** Define the patient's problem
  - Make specific & accurate diagnosis.
- **Step 2:** Consider the pathophysiological implication of the diagnosis
- **Step 3:** Specify the therapeutic objective.
- **Step 4:** Select the Drug of choice
- **Step 5:** Determine the appropriate dosing regimen.
- **Step 6:** Devise a plan for monitoring the drug's action and determine an end point for therapy.
- **Step 7:** Give information, instructions and warnings (patient education).
- **Finally,** your drug selecting criteria should be:
  - Efficacy, safety, suitability and cost of the medicine.

Prescription Writing

❖ OBJECTIVES:

At the end of this session a student should be able to:

- Identify the parts of a prescription and realize the importance of each.
- Write a prescription in the correct format.
- Understand the medico-legal importance of a prescription.

❖ Patient Five Rights:

- ✓ Right Patient: Diagnosis.
- ✓ Right Drug.
- ✓ Right Dose.
- ✓ Right Time.
- ✓ Right Route.

❖ Writing a prescription must be based on a series of rational steps:

1. Make a specific diagnosis (even if it is "presumptive").
2. Consider the pathophysiology of the diagnosis selected so that effective therapy may be instituted.
3. Select a specific therapeutic objective.
4. Select a drug of choice. This must be based on diagnosis, specific characteristics of the patient and the clinical presentation, laboratory tests (culture & sensitivity , hormone levels etc.) and cost.
5. Determine an appropriate dosing regimen. It must be determined primarily by the pharmacokinetics of the drug in the patient especially when the patient is known to have a disease of the major organs required for the metabolism or elimination of the drug selected.
6. Devise a plan for monitoring the drug's action and determine an end point for the therapy. The drug effects may be monitored based on lab tests, signs & symptoms
7. Plan a program of patient education.

❖ ELEMENTS OF A PRESCRIPTION:

- The prescription order is an important therapeutic transaction between the physician and the patient. It must communicate clearly with the pharmacist and adequately instruct the patient on how to take the prescribed medicine.

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- Prescription orders are medico legal documents. Therefore they must be written legibly in ink. The legal responsibility for prescribing lies in the doctor who signs the prescription. The prescription order consists of the following elements:
  - **Date.**
  - **Identity of the prescriber.**
  - **Identity of the patient.**
  - **Body of the prescription.**
  - **Signature.**

➢ DATE:

This is important due to its legal significance. It also enables the pharmacist to verify matters if too much time has elapsed since its writing.

➢ IDENTITY OF THE PRESCRIBER:

- Name
- License classification (Specialty).
- Address.
- Office telephone number (if any).

➢ IDENTITY OF THE PATIENT:

- Name
- Address.
- Age of the patient is a legal requirement especially in case of 'prescription - only medicines' for children under 12 years.
- Diagnosis.
- Sex (Gender).

➢ BODY OF THE PRESCRIPTION:

- The symbol Rx., is an abbreviation for `recipe', the Latin for `take thou'.
- Name of the drug, strength and dose
  - Names of drug and prescription should not be abbreviated, use approved titles only.
  - When writing the drug name, the generic name may be preferred.
  - If two or more drugs are prescribed, they may be written one below the other with the appropriate dosages.

- If the formulation has more than one ingredient, the principal drug is written first, and then the vehicle, the solvent for the solution or the bulking agent for a capsule goes last. In general practice, the following should be noted:

I. For solids, quantities of one gram or more should be written 1g etc.
   * If less than 1 gram, it must be written in milligrams (e.g. 500mg not 5g)
   * Avoid unnecessary zeros after decimal point (e.g. 1mg not 1.0mg).
   * When decimals are unavoidable, a zero must be written in front of the decimal point where there is no other figure (e.g. 0.5ml not .5ml).
   * Use of decimal point is acceptable to express a range (e.g. .5 - 1g).

II. Avoid misleading abbreviations. Always write 'units' not U, 'micrograms' not .ug, nanograms not ng.

III. Strength of the medication must be written in metric units. The term milliliter (ml or mL) may be used but not cubic centimeters (cc) or cm3.

IV. Dose and dose frequency should be stated, in case of preparations to be taken 'as required' a minimum dose interval should be prescribed. Avoid ambiguous direction like '1 ampoule of Fursemide' where ampoules of various strengths may be available.

✍ Direction to pharmacist, it may include directions like ` Dispense 100ml' ` Dispense with oral syringe' ` make a solution' ` Mix' etc.

✍ Directions to the patient:

- Must be drug specific and patient specific.
- Simple directions in Arabic are preferred.
- Avoid abbreviations. But recognized Latin abbreviations may be used.

➢ SIGNATURE:

The order must be signed (last name in full) in ink.

❖ COMMON PRESCRIBING ERRORS:

- Illegible
- Ambiguous directions
- Insufficient information
- Inappropriate prescription of drug

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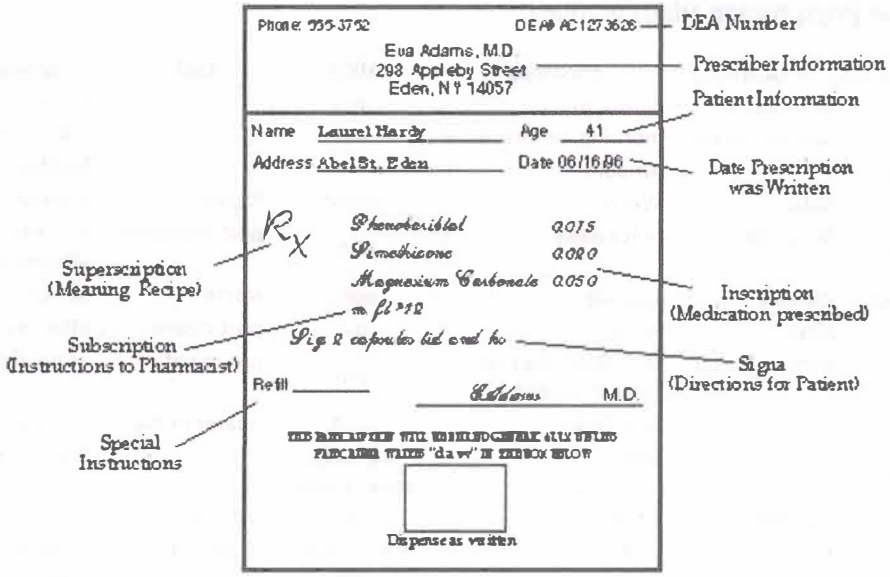
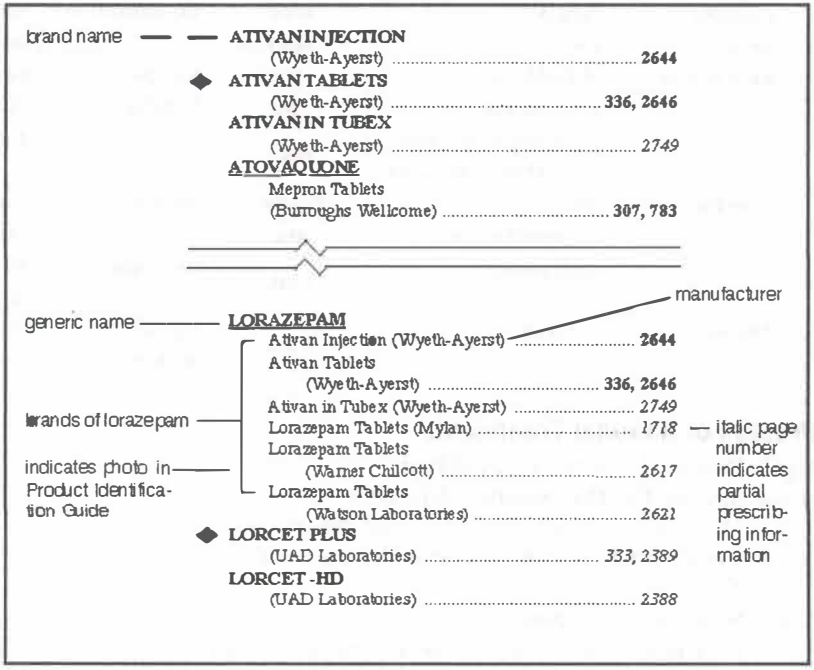
❖ Some Prescription Abbreviations:

Abbr.	Latin	Meaning	Abbr.	Latin	Meaning
a.c.	ante cibum	before meals	mcg		Microgram
a.m.	ante meridiem	morning, before noon	mg		Milligram
amp		Ampule	mL		Milliliter
aq	aqua	Water	nebul	Nebula	a spray
b.i.d.	bis in die	twice daily	p.m.	post meridiem	evening or afternoon
cap., caps.	capsula	Capsule	noct.	Nocte	at night
c	cibos	Food	p.c.	post cibum	after meals
cc	cum cibos	with food, (but also cubic centimetre)	prn	pro re nata	as needed
cf		with food	q.i.d.	quater in die	four times a day
elix.		Elixir	SC, subc, subq, subcut		Subcutaneous
emuls.	emulsum	Emulsion	sol	Solution	Solution
et	et	And	s.o.s., si op. sit	si opus sit	if there is a need
g		Gram	stat	Statim	Immediately
gtt(s)	gutta(e)	drop(s)	supp	suppositorium	Suppository
h, hr	hora	Hour	susp		Suspension
h.s.	hora somni	at bedtime	syr	Syrupus	Syrup
ID		Intradermal	tab	Tabella	Tablet
IM		intramuscular (with respect to injections)	tbsp		Tablespoon
inj.	injectio	Injection	troche	Trochiscus	Lozenge
IP		Intraperitoneal	tsp		Teaspoon
IV		Intravenous	t.i.d.	ter in die	three times a day
m, min	Minimum	a minimum	t.d.s.	ter die sumendum	three times a day

❖ The Process of Rational Treatment:

Step 1: Define the patient's problem
Step 2: Specify the therapeutic objective
What do you want to achieve with the treatment?
Step 3: Verify the suitability of your P-treatment
Check effectiveness and safety
Step 4: Start the treatment
Step 5: Give information, instructions and warnings
Step 6: Monitor (and stop?) treatment





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Section Two

EXPERIMENTAL PHARMACOLOGY

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STUDY OF THE ACTION OF DRUGS ON THE RABBIT'S EYE

❖ OBJECTIVES:

At the end of the practical class the student shall be able to:

- Instill drugs carefully into the rabbit's eye by the pouch method without injuring the cornea.
- Study the effects of drugs on the rabbit's eye.
- Record, analyze and interpret the observations obtained during the experiment.

➢ **Animals:** Rabbits.

➢ **Apparatus:** Droppers, measuring scale, torch, cotton wool, calculator (optional).

➢ **Drugs & solutions:**

- Saline drop
- Pilocarpine drop
- Atropine drop
- Phenylephrine 2.0%
- Lignocaine 2.0%.

❖ PROCEDURE:

Place the rabbit (No.1) on the table. Measure the diameter of both the pupils with the help of a scale. Observe the condition of the conjunctiva (congested or not) and elicit the corneal and light reflexes. Record your findings. In the left eye put one drop of saline and in the right eye one drop of eserine. Use the pouch method for instilling the drops. After adding the drops, the medial canthus should be pressed for 10 seconds. Record the following parameters at one minute, 5 minutes and 10 minutes after instilling the drug and saline.

❖ Parameters to be measured:

- Diameter of the pupil
- Light reflex
- Corneal reflex

Record your observations in a tabular form. Repeat the same procedure for atropine, phenylephrine and lignocaine on separate rabbits (Nos 2, 3 & 4).

❖ Presentation of data and analyses:

Pool the data from other groups and formulate appropriate table(s) to display the data. Analyze the data using appropriate statistical test(s) and draw conclusions. Make sure that table(s) is/are complete in all respects.

❖ QUESTIONS:

1) Name three miotics and three mydriatics used clinically and their important uses and contraindications?

2) Name some ocular local anaesthetics and indications for their use?

3) The stomach wash fluid taken from a case of poisoning produced pin point pupils when instilled into the eye of a rabbit. The intraocular tension was found to be decreased. What is your probable diagnosis? Justify your answer.

4) List the ophthalmological routes of administration? Draw a diagram to illustrate the sites.

STUDY OF EFFECT OF DRUGS ON FROG'S INTESTINE

❖ OBJECTIVES:

At the end of the practical class the student shall be able to:

- Demonstrate the action of drugs on intestine of frog.
- Record and interpret correctly the observations obtained.
- List uses of cholinergic and anticholinergic drugs and explain the basis for their use in each condition.

➢ **Animals:** Frog.

➢ **Apparatus:** A pair of scissors, forceps, cotton, frog board.

➢ **Drugs & solutions:**

- Neostigmine 0.5 mg/ml
- Atropine 0.5 mg/ml
- Ringer solution

❖ PROCEDURE:

Pith a frog. Cut small piece of small intestine and place it in ringer solution. Add 1 ml of neostigmine and notice the contraction of small intestine. Add 1 ml – 2 ml of atropine and notice the relaxation of intestine. Record the onset and duration of action.

EFFECT OF CARDIAC STIMULANTS & DEPRESSANTS ON PERFUSED RABBIT'S HEART

❖ OBJECTIVES:

At the end of the practical class the student shall be able to:

- Record the contractions of isolated rabbit's heart on a kymograph and demonstrate the effect of drugs on it.
- Interpret the observations and explain the basis for the same.
- List the cardiac stimulants & depressants and understand the rationale for their use in therapy.

➢ **Animals:** Rabbit.

➢ **Apparatus:** Rabbit heart perfusion apparatus, Student's physiograph / Starling's heart lever, smoked drum, syringes, needles.

➢ **Drugs & solutions:**

- Adrenaline HCl 0.5 mg/ml
- Calcium gluconate
- Neostigmine
- Atropine 0.5 mg/ml

❖ Preparation:

Rabbit is pithed, dissected, the heart is removed and perfused through the sinus venosus. Insert a curved needle in the apex of the heart and attach it to a Starling's heart lever. Record the contractions.

❖ PROCEDURE:

1. Note the normal heart rate, by counting each upstroke (systole) and downstroke (diastole) of the moving drum together as one beat for 1 minute, force of contraction (by measuring the amplitude or height of the contraction from the baseline with a scale), tone (by observing shift in the baseline) and the cardiac rhythm (by observing any irregularity in the contractions).

2. Inject 0.2 ml of drugs 1-4 in succession (cardiac stimulants) in the tube through which the heart is being perfused and record the responses. A control reading (without addition of any drug) should be taken before and after each drug response. All the parameters mentioned above should be recorded during the control and drug responses respectively. The heart rate, drug name and the dose

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should be mentioned in the recording during the control and drug responses. The next drug response should be recorded only after the heart rate has returned to the approximate original value. In case the heart stops because of systolic or diastolic arrest produced by a cardiac depressant the drum should be stopped and re-started only when the heart is contracting. In case adequate response is not observed use a higher dose.

3. Inject 0.2ml of propranolol (depressant) and note its response. Stop the drum for 5 minutes. After 5 minutes inject adrenaline (same dose as injected previously) and note whether its effect is adequately blocked. In case sufficient blockade is not obtained repeat the procedure with 0.4ml propranolol and also see that the 5 minutes duration is adhered to.

4. Inject Calcium chloride immediately after adrenaline effect has been blocked, and note whether its effect has been blocked or not. In case the typical increase in time and /or systolic arrest is not observed use higher dose.

5. Inject 0.2 ml of drugs 6&7 in succession (cardiac depressants) i.e acetylcholine and potassium chloride after taking control readings in between drug responses. Note also the condition of the heart during systole arrest (contracted) and diastolic (dilated).

6. Inject 0.2 ml of Atropine and note its response. Normally no response is seen because it is an in vitro preparation and moreover atropine has no intrinsic activity of its own. Stop the drum and wait for 5 minutes, inject acetylcholine (same dose as given earlier) and note whether effect is completely blocked. In case sufficient blockade is not obtained, repeat the same procedure with 0.4ml of atropine and see that the 5 minutes duration is adhered to.

7. Finally inject potassium chloride after the effect of acetylcholine has been blocked by atropine and note whether the effect is blocked. There should be no blockade of KCl effect.

8. Tabulate your observations.

9. Pool the data from all the other groups and apply a suitable statistical test. Write down the conclusions and inferences.

HYPERACTIVITY OF MUSCRINIC RECEPTORS

❖ OBJECTIVES:

At the end of the practical class the student shall be able to:

- Calculate and measure the exact quantity of drug to be injected to the animal.
- Administer the drugs by the subcutaneous route to rabbits.
- Identify and record experimentally induced writhing in rabbits.
- Tabulate observations and draw suitable inferences from the experiment.

➢ **Animals:** Rabbit.

➢ **Apparatus:** Syringe (with 100 divisions) 26g needle.

➢ **Drugs & solutions:**

- Neostigmine 0.5 mg/ml
- Atropine 0.5 mg/ml

❖ PROCEDURE:

1. Inject 0.5 mg/kg subcutaneous of neostigmine to the rabbit.
2. Note the onset of action and record your observation.
3. After 30 minutes inject 0.5 mg/kg subcutaneous of atropine to the rabbit.
4. Note the response and record your observation.

STUDY OF GENERAL ANESTHETIC EFFECT IN RABBITS

❖ General Anesthesia:

Is a state of reversible C.N.S. inhibition characterized by loss of consciousness, sensation and motor activity to an extent allowing the performance of easy and painless operation.

General Anesthesia aims to ensure unconsciousness, amnesia, analgesia, relaxation of skeletal muscles and loss of control of reflexes of the autonomic nervous system.

❖ Stages of General anesthesia:

➢ First stage (Induction, analgesia):

- ✓ **Begins:** by administration of drug.
- ✓ **In between:** increased sense of hearing, analgesia and normal blood pressure, normal pupil size, and +ve light reflex.
- ✓ **End:** when consciousness is lost.

➢ Second stage (Excitement, delirium):

- ✓ **Begins:** by loss of consciousness then excitation.
- ✓ **In between:** delirium, excitation, uncontrolled movement, potential for vomiting, mydriasis with +ve light reflex, laryngeal spasm, hypertension and tachycardia.
- ✓ **End:** normalization of respiration and circulation.

➢ Third stage (Surgical anesthesia):

- ✓ **Begins:** when respiration becomes regular , BP returns to normal, normal size of pupil and loss of eye lid and conjunctival reflex, eye ball roll then fixed.
- ✓ **In between:** absence of movement, no pain reflex.
- ✓ **End:** when respiration stopped.

➢ fourth stage (Medullary paralysis):

- ✓ **Begins:** by stop of respiration.
- ✓ **In between:** hypotension, very weak pulse, diluted nonreactive pupils.
- ✓ **End:** by circulatory failure and then death if there is no circulation and respiratory support.

NOTES

General anesthesia usually involves the administration of different drugs for:

A.Pre-anesthetic medications: drugs used before G. anesthetic agent to make safe and more agreeable anesthesia to the patient.

Examples: Anxiolytics, Sedatives, Narcotic analgesics, Antiemetics, Mascarinic antagonists, muscle relaxants, antihistamine, alph 2 agonists, antimicrobial....

Aims of their uses:

1- Sedation to reduce patient anxiety.
2- Additive or synergistic effect to reduce the dose of G. anesthetic, decrease the side effects, relieve from pain and to induce smooth, rapid induction.
3- Prevent the postoperative nausea, vomiting, pain, hypertention,....etc.

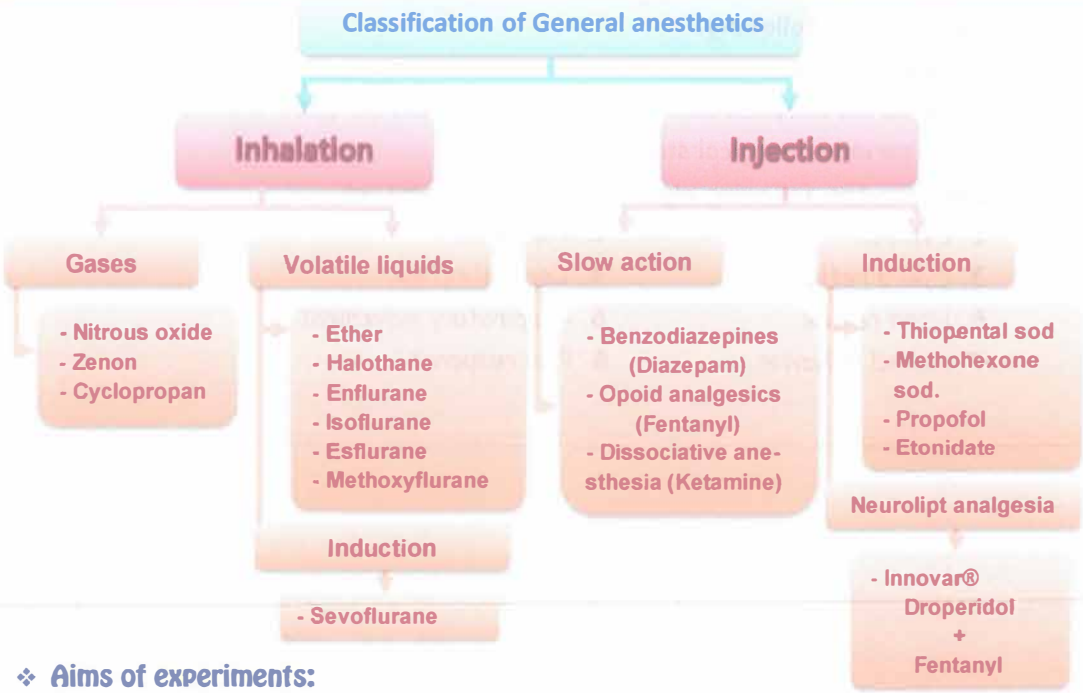
B.Induction of anesthesia: commonly by intravenous or inhalation anesthetics

Examples: Propofol, Etomidate, Ketamine, Thiopentone, ... , sevoflurane.

C.Maintenance of anesthesia: by allowing the patient to breathe a carefully controlled mixture of oxygen, nitrous oxide and a volatile anesthetic agent (halothane) or by having a carefully controlled infusion of medication (Propofol), through an IV catheter injected by autoinjector.

D.Monitoring: containueous monitoring of cardiovascular and respirapry systems and body fluids.

E.Post-anesthetic medications: drugs used to releive pain, stop N/V prophylaxis of microbial infection.



❖ Aims of experiments:

To notice the stages of general anesthesia and to evaluate the general anesthetic activity of:

1- Ether inhalation in rabbit.

2- Ketamin injection in rabbit.

- **Experiment 1:**

-Materials: Rabbit, Ether, alcohol pads, glass-cage.

-Route of administration: Inhalation.

-Procedure: Put the rabbit inside the glass-case , wetting the cotton with ether and place it on the nose of rabbit and observed the stages of general anesthesia.

- **Experiment 2:**

-Materials: Rabbit, Ketamin vial (20-50mg/ kg), alcohol pads.

-Route of administration: IM.

-Procedure: Handle the rabbit for IM injection then clean the site of inj. by alcohol pads and inject Ketamin 40 mg / kg and notice the stages of general anesthesia.

- **Measure the following:**
  - Induction time.
  - The period between administration of drug and disappearance of drug effect.
  - The period of surgical stage.
- **Look for the following signs during the experiment:**

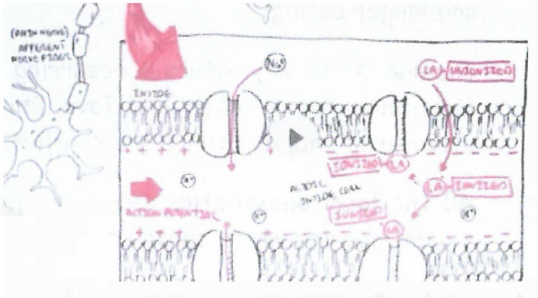
1. Eye ball
2. Pupil size
3. Eyelid reflex
4. Corneal reflex
5. Light reflex
6. Respiratory movement
7. Animal behavior
8. Pain response.

LOCAL ANESTHETICS

❖ Definition:

Are drugs that reversibly prevent the generation and conduction of nerve impulse at the site of administration of these drugs without loss of consciousness or structural damage to neurons.

❖ Mechanism of action:



Local anesthetics bind with sodium channel (from the intracellular side of Na+ channel) this will block sodium channel leading to inactivation of sodium channels and preventthe rapid influx of Na+ ion essential for nerve pulse transmission across the nerve cell membrane. This blockage leads to stop generation and conduction of nerve impulse which as a result stop pain sensation at the area of drug administration.

❖ Classification:

➢ Esters:

- They have short duration of action.
- They are metabolized in the plasma via pseudocholinesterases.
- They are much more likely than amides to cause allergic hypersensitivity reactions.
- Commonly used esters include: cocaine, procaine, tetracaine, chloroprocaine, and benzocain.

➢ Amides:

- They have long duration of action.
- They are metabolized in the liver by cytochrom P450.
- They are more stable in solution than esters.
- Commonly used amides include: lidocaine (lignocaine), mepivacaine, prilocaine, bupivacaine, and ropivacaine.

NOTES

- **Natural toxins** cause local anesthesia but with different mechanism where they bind the sodium channel from the extracellular side of Na+ channel.E.g: Saxitoxin and Tetrodotoxin.
- **Ropivacaine and levobupivacaine,** represent exploitation of the S enantiomer of these chemicals to create anesthetics which are less toxic, more potent, and longer acting.
- **Cocaine** is the only naturally occurring local anesthetic indigenous to the Andes Mountains, West Indies, and Java. It was the first anesthetic to be discovered and; all others are synthetically derived.
- **All the local anesthetics** cause vasodilation at the site of administration except cocaine which cause vasoconstriction.
- **Local anesthetics have basic nature** so their effect decrease at acidic medium as happens in the infected areas.
- **Local anesthetics are less effect at infected tissues** due to:
  1. Acidic formed medium.
  2. Increased blood supply at infected tissue.

❖ Prolongation of action of local anesthetics:

To prolong the duration of action of local anesthetic you have to decrease their absorption from the site of administration to the systemic circulation by **vasoconstrictor** such as epinephrine is added, but do not use the mixture in areas of extremities or end organs such as fingers, toes, ear lobes, nose and penis. Because that may lead to ischemia and necrosis.

❖ Function lost with local anesthetics depending on concentration:

1. Pain perception.
2. Temperature sensation.
3. Touch sensation.
4. Skeletal muscle tone.
5. Proprioception.

❖ Routes of local anesthetics administration:

➢ Topical (Surface) application:

- Direct use of drug on the surface of skin or mucous membranes such as in wounds, ulcers, ..etc.
- They are available as cream, gel, ointment, liquid (as drops, mouth wash, ..), or spray.

➢ Local injection:

1. **Infiltration** (injection of local anesthetic by SC route)
2. **Regional anesthesia:**
   a. Brachial plexus block involves the injection of local anesthetic agents in close proximity to the brachial plexus, temporarily blocking the sensation and ability to move the upper extremity.
   b. Intravenous regional anesthesia (Bier's block): Injection of local anesthetic and placement of the tourniquet, used in short operative procedures for the extremities.
3. **Epidural block:** drug is injected into the epidural space of the spinal cord. Injection may be performed anywhere along the vertebral column (cervical, thoracic, lumbar, or sacral).
4. **Spinal anaesthesia** is a technique whereby a local anaesthetic drug is injected into the cerebrospinal fluid. Injections are typically performed below the second lumbar vertebral body to avoid piercing and consequently damaging the spinal cord.

Practical Part: (Evaluation Of Local Anesthetics On Human)

❖ Topical application method:

➢ Materials:

- **Drug:** Lidocaine 10% spray.
- **Test tube 1:** contain cold water.
- **Test tube 2:** contain hot water.

➢ Procedures:

1. By your tongue test the sensation to cold and hot water before drug administration.
2. Spray two puffs of lidocaine 10% on to the top of your tongue.
3. Retest your tongue sensation by the cold and hot water in the test tubes.
4. Record your results including: Onset of action, duration of action.

*** Use the following table to record your work: as (+ve) or (-ve).**

Time interval	Tongue sensation to hot tube	Tongue sensation to cold tube
Zero Time		
3 minutes		
6 minutes		
9 minutes		
12 minutes		
20 minutes		

❖ Local injection method:

➢ Materials:

- **Drug:** - Lidocaine 2% vials.
  - Lidocaine + Adrenaline mixture vials.
- Syring (3cc) and Pin.
- Alcohol pads.

➢ Procedures:

1. Pinch by the pin your arm skin to measure your normal pain sensation.
2. Inject 1 cc subcutaneously of lidocaine 1% in the right arm and in the left arm inject 1 cc of mixed lidocaine and adrenaline.
3. Measure your pain sensation periodically in both arms.
4. Record your results including: Onset of action, duration of action.

*** Use the following table to record your work: as (+ve) or (-ve).**

Time interval	Pain sensation with lidocaine	Pain sensation with mixture
Zero Time		
1 minutes		
5 minutes		
10 minutes		
20 minutes		
30 minutes		
1 hour		

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EFFECT OF DRUG ON BLOOD SUGAR

❖ OBJECTIVES:

At the end of the practical class the student shall be able to:

- Calculate and measure the exact quantity of drug to be injected to the animal.
- Administer the drugs by the subcutaneous and intraperitoneal routes to rabbits
- Identify and record experimentally induced writhing in rabbits.
- Tabulate observations and draw suitable inferences from the experiment.

➢ **Animals:** Rabbit.

➢ **Apparatus:** Syringe (with 100 divisions) 26g needle.

➢ **Drugs & solutions:**

- Mixtard insulin
- Soluble insulin
- Glepenclamid
- Dexamethasone
- Normal saline

❖ PROCEDURE:

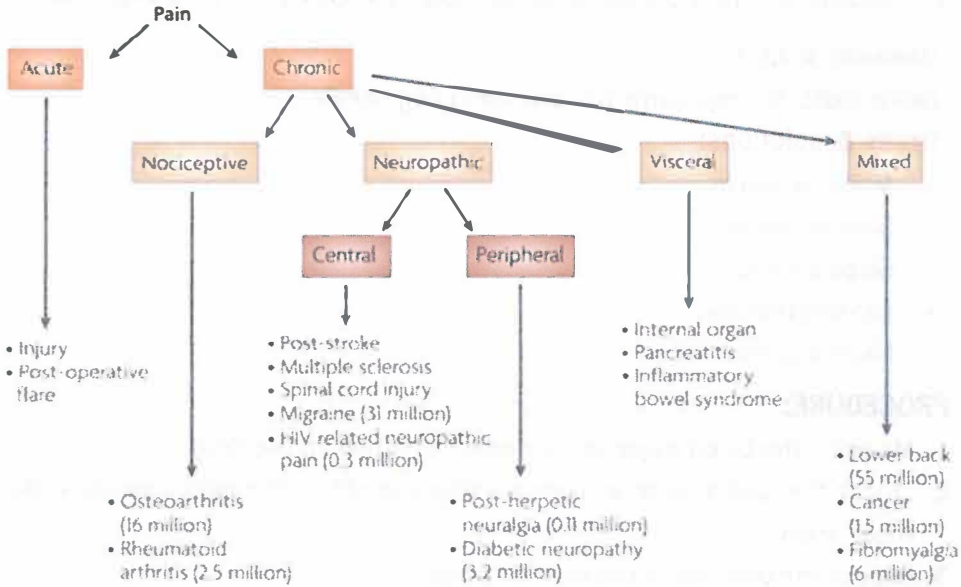
1. Measure the blood sugar before administration of the drug.
2. Inject the rabbit by drug: normal saline and after 30 minutes measure the blood sugar again.
3. Repeat the previous steps with all drugs.
4. Place the data on table and discuss the results.

STUDY OF ANALGESICS

❖ Definitions:

➢ **Analgesics:** A drug that selectively relieves pain sensation (perception) by acting in the CNS or on peripheral pain mechanisms, without significantly altering consciousness.

➢ **Pain (Algesia):** is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.



➢ **Inflammation:** is part of the complex biological protective response of body tissues to harmful stimuli, such as pathogens, damaged cells, or irritants.

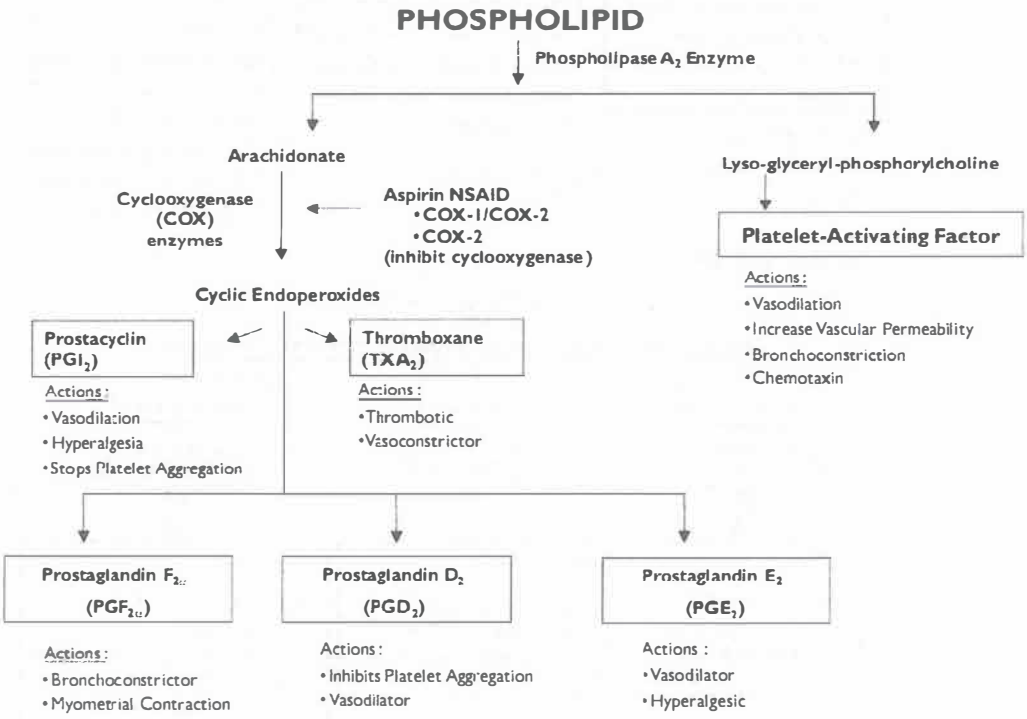
❖ Types Of Analgesics:

➢ Peripheral Analgesics:

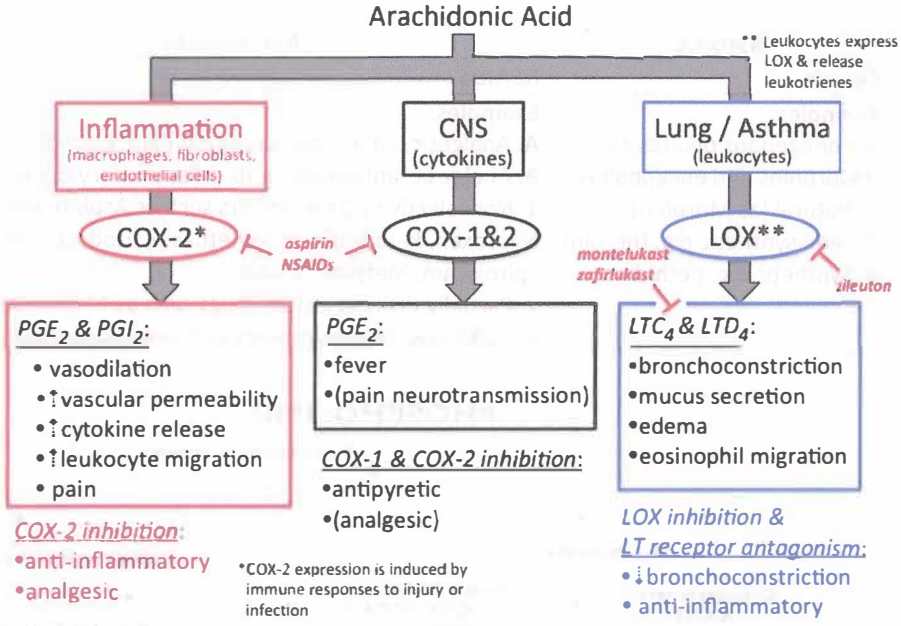
Causal	Non-causal
Treat the cause	**Does not treat the cause**
Examples: 1. Atropine relief colic(antispasmodic). 2. Ergotamine treat migraine. 3. Colchicines treat gout.	**Examples:** 1. Local anesthetics (for superficial tumor). 2. Counter-irritant (apply pain that counteract or mask the original one e.g. acupuncture).

➢ Centeral Analgesics:

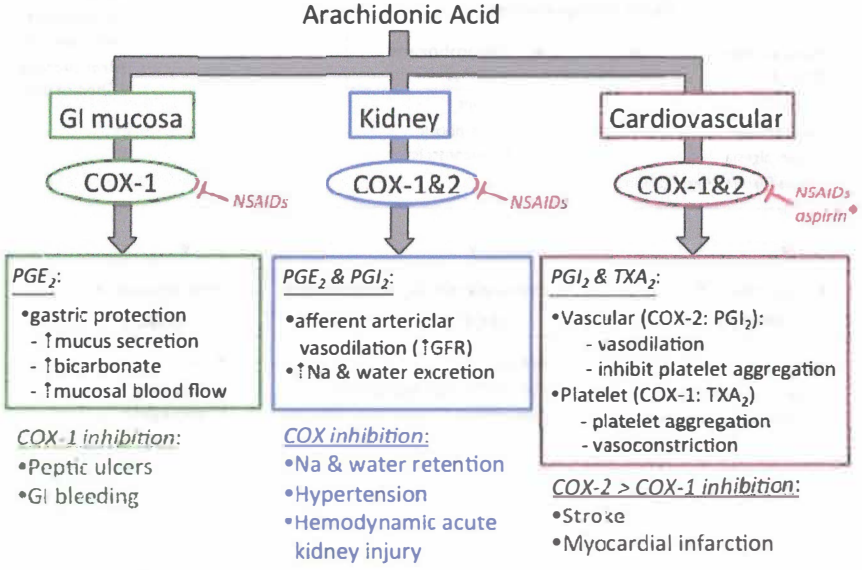
Narcotic	Non-narcotic
Opoids	**NSAIDs**
Examples: 1. Endogenous opiates as endorphins and encephalins. 2. Natural (as Morphin) 3. Semi synthetic e.g. (heroin) 4. Synthetic e.g. pethidine.	**Examples:** **A.** Analgesic, antipyretic drugs e.g Paracetamol. **B.** Analgesic, antipyretic, anti-inflammatory drugs e.g.: 1. Nonselective COX inhibitors such as Aspirin, Ibuprofen, Naproxen, ketoprofin, indomethacin, Etodolac, diclofenac , piroxicam, Mefenamic acid. 2. Partially COX2 selective drugs such as Meloxicam. 3. COX2 selective drugs such as "coxibs" Celecoxib.



Anti-inflammatory Mechanisms:



NSAID Side Effects:



◆ Low dose aspirin irreversibly inhibits platelet COX-1

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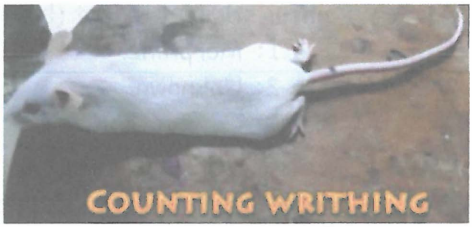
Practical Part

❖ Writhing Test:

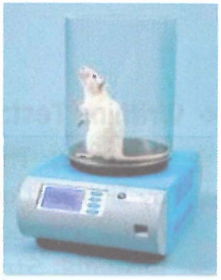


- **Principle:** The painful stimulus is induced by IP injection of an irritant substance (e.g. acetic acid)
- **Writhing:** Stretching of the body, with-drawing of the limb, retraction of the abdomen & the stomach touches the ground
- **Materials:**
  - **Animal:** Mice
  - **Painful stimulus:** Chemicals e.g. acetic acid (0.6%) solution in a dose of 1 ml/100 gm IP.
  - **Drug used:** NSAID e.g. Na salicylate (2%); dose1= 100 mg/kg, dose2= 200 mg/kg IP.
- **Method:**
  1. Weigh three mice (one mouse is control i.e. given acetic acid only; the other two mice are treated with 100mg/kg Na salicylate and 200mg/kg Na salicylate, respectively)
  2. Calculate the dose of acetic acid for each animal & the doses of Na salicylate for the two treated mice
  3. Inject the calculated doses of Na salicylate IP to the animals and inject the control with acetic acid IP. 5min. later inject the calculated doses of acetic acid to the animal pretreated with Na salicylate IP.
  4. The mice then are observed and the time needed by the animal to writhe is recorded. The number of writhings in 10 minutes for each animal is recorded in the table:

Drug injected	Onset of action	Number of writhing/10min

❖ Hot Plate Method:

- **Principle:** is a test of the pain response in animals, similar to the tail flick test. It is used in basic pain research and in testing the effectiveness of analgesics by observing the reaction to pain caused by heat.



➢ Materials:

- **Animal:** 12 Mouse.
- **Instrument:** Hot plate analgesiometer and 1000ml beaker.
- **Painful stimulus:** Heat (55°C).
- **Drug 1:** Morphine.
- **Drug 2:** Unknown.

➢ Method:

1. The animals are weighed to the nearest gm. Then the mice will be divided into two groups (each group had 6 mice), the groups are labeled I, II.
2. The sensitivity to pain of all animals is tested on the hot plate (55°C) before theadministration of any drug by measuring their reaction time (licking of their leg or jumping outof beaker), it should not exceed 10 seconds.
3. To group I (morphine group) morphine (0.5 mg/ml) is given in a dose of 0.2ml/ 10 gm wt. intraperitoneally. Then the sensitivity of each mouse is tested every 10 min. following the injection till recovery.
4. To group II, unknown group, unknown is given in a dose of 0.2ml/10 gm wt intraperitoneally. Then the sensitivity of each mouse is tested every 10 min. following the injection till recovery.
5. The results are recorded in tables.
6. Draw the curve of results.

Time interval	Pain response (latency time) Group I	Pain response (latency time) Group II
Before injection		
After injection		
10 minutes		
20 minutes		
30 minutes		
40 minutes		
50 minutes		
60 minutes		

The time of latency is defined as the time period between the zero point, when the animal is placed on the hot plate surface, and the time when the animal licks its paw or jumps off to avoid thermal pain.

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ADVERSE EFFECTS OF DRUGS & SENSITIVITY TEST

❖ ADVERSE EFFECTS OF DRUGS:

- As used, the term adverse effects refers to any undesired responses to drug administration, as opposed to therapeutic effects, which are desired responses. Most drugs produce a mixture of therapeutic and adverse effects; all drugs can produce adverse effects. Adverse effects may produce esentially any sign, symptom, or disease process and may involve any body system or tissue.
- They may be common or rare, mild or severe, localized or widespread, depending on the drug and the recipient.
- Some adverse effects occur with usual therapeutic doses of drugs (often called side effects); others are more likely to occur and to be more severe with high doses.
- **Common or serious adverse effects include the following:**

1. **CNS effects** may result from CNS stimulation (eg, agitation, confusion, delirium, disorientation, hallucinations, psychosis, seizures) or CNS depression (dizziness, drowsiness, impaired level of consciousness, sedation, coma, impaired respiration and circulation). CNS effects may occur with many drugs, including most therapeutic groups, substances of abuse, and over-the-counter preparations.
2. **Gastrointestinal effects** (anorexia, nausea, vomiting, constipation, diarrhea) are among the most common adverse reactions to drugs. Nausea and vomiting occur with many drugs from local irritation of the gastrointestinal tract or stimulation of the vomiting center in the brain. Diarrhea occurs with drugs that cause local irritation or increase peristalsis. More serious effects include bleeding or ulceration (most often with aspirin and nonsteroidal anti-inflammatory agents) and severe diarrhea/colitis (most often with antibiotics).
3. **Hematologic effects** (blood coagulation disorders, bleeding disorders, bone marrow depression, anemias, leukopenia, agranulocytosis, thrombocytopenia) are relatively common and potentially life threatening. Excessive bleeding is most often associated with anticoagulants and thrombolytics; bone marrow depression is usually associated with antineoplastic drugs.
4. **Hepatotoxicity** (hepatitis, liver dysfunction or failure, biliary tract inflammation or obstruction) is potentially life threatening. Because most drugs are metabolized by the liver, the liver is especially susceptible to drug-induced injury. Drugs that are hepatotoxic include acetaminophen (Tylenol), isoniazid (INH), methotrexate (Mexate), phenytoin (Dilantin), and aspirin and other

salicylates. In the presence of drug- or disease-induced liver damage, the metabolism of many drugs is impaired. Consequently, drugs metabolized by the livertend to accumulate in the body and cause adverse effects. Besides hepatotoxicity, many drugs produce abnormal values in liver function tests without producing clinical signs of liver dysfunction.

5. **Nephrotoxicity** (nephritis, renal insufficiency or failure) occurs with several antimicrobial agents (eg, gentamicin and other aminoglycosides), nonsteroidal anti-inflammatory agents (eg, ibuprofen and related drugs), and others. It is potentially serious because it may interfere with drug excretion, thereby causing drug accumulation and increased adverse effects.
6. **Hypersensitivity or allergy** may occur with almost any drug in susceptible clients. It is largely unpredictable and unrelated to dose. It occurs in those who have previously been exposed to the drug or a similar substance (antigen) and who have developed antibodies. When readministered, the drug reacts with the antibodies to cause cell damage and the release of histamine and other intracellular substances. These substances produce reactions ranging from mild skin rashes to anaphylactic shock. Anaphylactic shock is a life-threatening hypersensitivity reaction characterized by respiratory distress and cardiovascular collapse. It occurs within a few minutes after drug administration and requires emergency treatment with epinephrine. Some allergic reactions (eg, serum sickness) occur 1 to 2 weeks after the drug is given.
7. **Drug fever** is a fever associated with administration of a medication. Drugs can cause fever by several mechanisms, including allergic reactions, damaging body tissues, increasing body heat or interfering with its dissipation, or acting on the temperature regulating center in the brain. The most common mechanism is an allergic reaction. Fever may occur alone or with other allergic manifestations (eg, skin rash, hives, joint and muscle pain, enlarged lymph glands, eosinophilia) and its pattern may be low grade and continuous or spiking and intermittent. It may begin within hours after the first dose if the client has taken the drug before, or within approximately 10 days of continued administration if the drug is new to the client. If the causative drug is discontinued, fever usually subsides within 48 to 72 hours unless drug excretion is delayed or significant tissue damage has occurred (eg, hepatitis). Many drugs have been implicated as causes of drug fever, including most antimicrobials, several cardiovascular agents (eg, beta blockers, hydralazine, methyldopa, procainamide, quinidine), drugs with anticholinergic properties (eg, atropine, some

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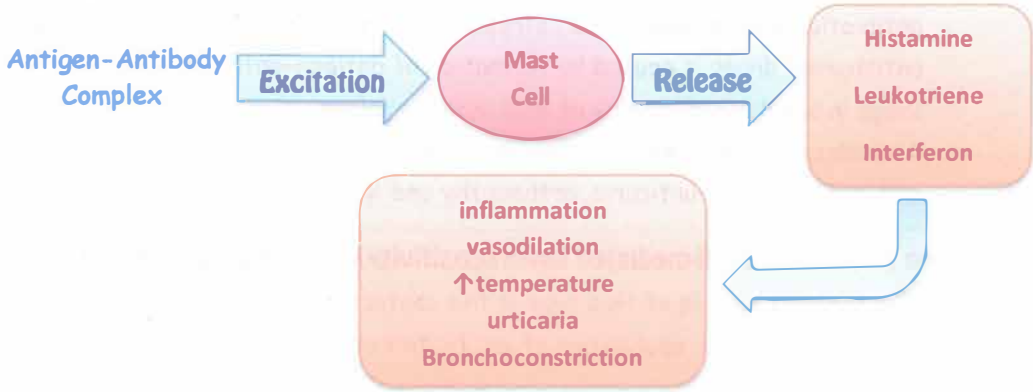
antihistamines, phenothiazine antipsychotic agents, and tricyclic antidepressants), and some anticonvulsants.

8. **Idiosyncrasy** refers to an unexpected reaction to a drug that occurs the first time it is given. These reactions are usually attributed to genetic characteristics that alter the person's drug-metabolizing enzymes.
9. **Drug dependence** may occur with mind-altering drugs, such as opioid analgesics, sedative-hypnotic agents, antianxiety agents, and CNS stimulants. Dependence may be physiologic or psychological. Physiologic dependence produces unpleasant physical symptoms when the dose is reduced or the drug is withdrawn. Psychological dependence leads to excessive preoccupation with drugs and drug seeking behavior.
10. **Carcinogenicity** is the ability of a substance to cause cancer. Several drugs are carcinogens, including some hormones & anticancer drugs. Carcinogenicity apparently results from drug-induced alterations in cellular DNA.
11. **Teratogenicity** is the ability of a substance to cause abnormal fetal development when taken by pregnant women. Drug groups considered teratogenic include analgesics, diuretics, antiepileptic drugs, antihistamines, antibiotics, antiemetics, and others.

❖ Anaphylactic Reactions:



➢ Type I hypersensitivity (5-10 minutes):

- These reactions are most common in patients with a history of anaphylaxise with drugs, foods (such as nuts) or insect stings, and in atopic individuals with a history of asthma and eczema.
- Typically, anaphylaxis occurs on the second or third exposure to the drug, and may occur following administration of only very small amounts. The mechanism

involves recognition of the drug (or a drug-protein complex) by IgE molecules on the surface of mast cells and subsequent degranulation with release of histamine and other inflammatory mediators.

- The onset of the clinical syndrome of anaphylaxis is often rapid. Prompt recognition and treatment can be lifesaving.
- Penicillin antibiotics are notorious for causing anaphylaxis, even thought the incidence of severe reactions is very low. Other likely causes are radiopaque contrast media, local anaesthetics and streptomycine.

➢ Type II reactions (6-36 hours):

- These reactions occur owing to interaction between the drug and a circulating or membrane-bound protein to cause production of a circulating antibody of IgG or IgM class to causes haemolytic anemia e.g. methyldopa and penicillin, quinine.

➢ Type III (arthus, serum sickness or immune complex) reaction (4-12hrs):

- This type of reaction occur most commonly following injections of foreign serum to treat infectious disease (e.g. antitetanus serum). It also occurs with antibiotics such as penicillins , streptomycin and sulphonamides, as well as the antithyroid drugs it caused by formation of antigen-antibody complex which lodge in small blood vessels of skid, kidney, joints.
- This classic clinical presentation occurs several days following starting therapy and include fever, urticaria, arthopathy and lymphadenopathy, skin rash.

➢ Type IV reaction (cell-mediated hypersensitivity) (delayed 48-72 hours):

- The typical example of this type is the contact dermatitis which sometimes produced following application of antibiotics or other topical therapy on the skin.

➢ Clinical Features (Rapid and Dramatic):

- Bronchospasm causing breathlessness.
- Facial and laryngeal edema.
- Hypotension causing dizziness and collapse.
- Nausea, vomiting and diarrhea.

➢ Treatment:

1. Lay the patient down and raise the feet.
2. Ensure the airway is free.
3. Monitor blood pressure.
4. Give in following order:
   a. 1.1 ml of 1/1000 adrenaline I.M & repeat after 10-20 min if shock persist
   b. Antihistamine such as chlorpheniramine 10 mg I.V
   c. Hydrocortisone 100 mg I.V
5. If hypotension persist give a rapid intravenous infusion of 1-2 liter.
6. If hypoxia is severe oxygen or assisted ventilation may be necessary.

DRUGS AND PREGNANCY

During pregnancy, some medications are save & some are not depending on the passage of drug through yolk sac and placenta, and the nature of drug (teratogenic or not teratogenic) and some required a higher dose than usual and some dose change with the advancing pregnancy all these because of pharmacokinetic changes in pregnancy, by the embryo or fetus and by placenta.

* **Note:** we have to know the adaptations that occur during pregnancy and cause a lot of physiological, pharmacokinetic and anatomical changes.

Drugs in general should be given only if the potential benefit justifies the potential risk to the fetus.

❖ Drugs taken during pregnancy can affect the fetus in several ways:

1. They can act directly on the fetus, causing damage, abnormal development (leading to birth defects), or death.
2. They can alter the function of the placenta, usually by causing blood vessels to narrow (constrict) and thus reducing the supply of oxygen and nutrients to the fetus from the mother. Sometimes the result is a baby that is underweight and underdeveloped.
3. They can cause the muscles of the uterus to contract forcefully, indirectly injuring the fetus by reducing its blood supply or triggering preterm labor and delivery.

❖ Potential Problems During Pregnancy:

- Decreased fetal breathing, Delayed development of the nervous system, Facial feature abnormalities, especially during the third through sixth weeks following fertilization.
- Beginning in the fourth week - rapid cardiac development. Exposure to alcohol may result in atrial and/or ventricular abnormalities, issues with valve formation, and a potential increase in the risk for heart disease in adulthood.
- Sixth and seventh weeks - the corpus callosum, the structure that divides the left and right hemispheres of the brain and is responsible for communication between the two hemispheres , is most vulnerable to alcohol exposure. Exposure to alcohol may lead to its incomplete development, thus resulting in issues with neural communication.

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- After 8 weeks gestation, the fetus is not as vulnerable to organ-specific birth defects. The central nervous system overall, however, remains vulnerable, as well as the overall growth of the fetus. Infertility, miscarriage, stillbirth, low birth weight, preterm delivery.

❖ How a drug affects a fetus depending on:

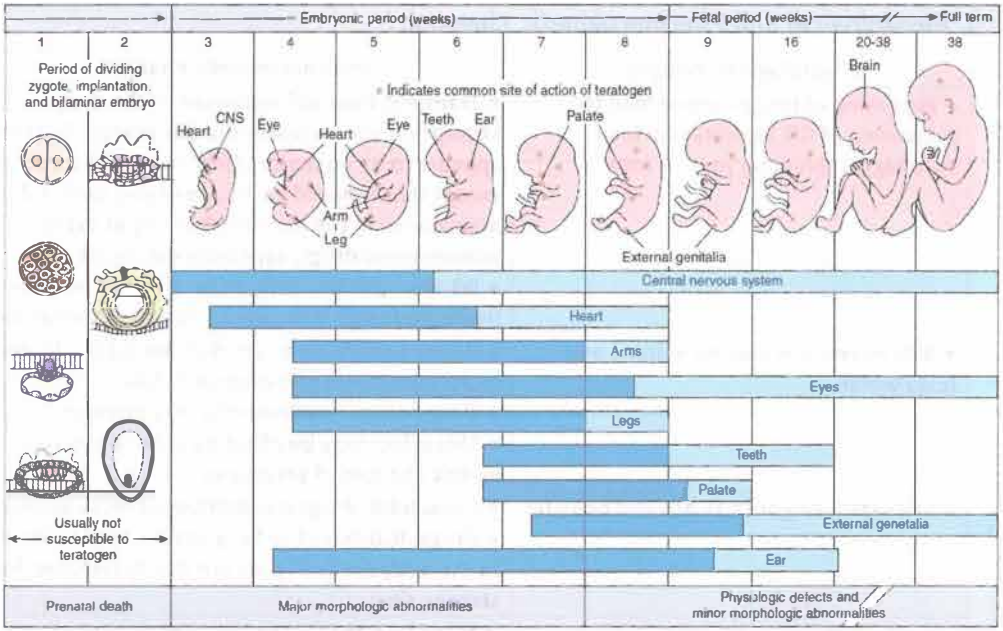
I. Physiological and Pharmacokinetic changes:

Physiological changes	Pharmacokinetic changes
• Increasing of Progesterone lead to decreasing of GIT motility and lower esophageal sphincter muscle tone.	• Transient time will increased so the drug absorption will increase too, but practically there appears to be no major effect in drug absorption except that reduced gastric emptying delays the appearance in the plasma (↑Tmax) of orally administered drugs, especially during labor. • IM absorption is likely to be efficient because tissue perfusion is increased due to vasodilatation.
• 50% Increase in plasma volume and body water.	• Water soluble drugs are distributed & "diluted" more than in the non-pregnant state. • Drug dosage requirements may increase. • This effect may be offset by other pharmaco-kinetic changes of pregnancy.
• Increased weight (~ 14 Kg) and body fat	• Fat-soluble drugs are distributed more widely. • Drugs distributed to fatty tissues tend to linger in the body because they are slowly released from storage sites.
• Decreased serum albumin. • The rate of albumin production is increased. However, serum levels fall because of plasma volume expansion. • Many plasma protein-binding sites are occupied by hormones that increase during pregnancy.	• More free drug is available for therapeutic or adverse effects on the mother and for placental transfer to the fetus. • A given dose of a drug is likely to produce greater effects than it would in the non-pregnant state.
• Increased renal blood flow and glomer-ular filtration rate secondary to increased cardiac output.	• Increased excretion of drugs by the kidneys, especially those excreted primarily unchanged in the urine (digoxin, lithium). • In late pregnancy, the increased size of the uterus decreases renal blood flow in supine position, This results in decreased excretion and prolonged effects of renally excreted drugs.

*These changes will effect on the drug kinetic and so the dose given for pregnant.

II. FETUS STAGE OF DEVELOPMENT AND ITS ACTIVITY:

Certain drugs taken early in pregnancy (within 20 days after fertilization) may act in an all-or-nothing fashion, killing the fetus or not affecting it at all.
During this early stage, the fetus is highly resistant to birth defects. However, the fetus is particularly vulnerable to birth defects between 3rd and 8th week after fertilization.



*The more active fetus the more drug passage throughout the placenta.

III. PLACENTAL TRANSFER OF DRUGS:

The placenta is not a perfect barrier to drugs & chemicals administered to mother. Placenta is capable of transferring drugs to the fetus with potential to great harm, on other hand, placental transfer of drugs administered to mother has been used to treat fetal arrhythmias, congestive heart failure, & other conditions.

➢ Factors affecting placental drug transfer and fetal tissues:

1. Physicochemical properties of drug.
2. Rate at which drug crosses placenta & amount of drug reaching the fetus.
3. Duration of exposure to drug.
4. Distribution characteristics in different fetal tissues.
5. Stage of placental & fetal development at time of exposure to the drug.
6. Effects of drugs used in combination.

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IV. DRUGS NATURE (TERATOGENESIS):

A teratogen is a chemical substance that can induce a malformation during development.

➢ Principles of teratology:

- Teratogens act with specificity. A teratogen produces a specific abnormality or constellation of abnormalities. E.g. thalidomide produces phocomelia, and valproic acid produces neural tube defects.
- Teratogens demonstrate a dose-effect relationship. Teratogens must reach the developing conceptus in sufficient amounts to cause their effects.
- The effect that a teratogenic agent has on a developing fetus depends upon the stage during development when the fetus is exposed.

➢ Mechanisms of Teratogenesis:

- Genetic interference, gene mutation, chromosomal breakage, interference with cellular function, enzyme inhibition, and altered membrane characteristics.
- The response of the developing embryo to these insults is failure of cell-cell interaction crucial for development, interference with cell migration, or mechanical cellular disruption.

➢ Some examples of teratogenes and FDA classifications:

DRUG	EFFECT (abnormality)
Thalidomide	Phocomelia, multiple defects.
Anticancer (methotrexate)	Cleft palate, hydrocephalus, fetal death, multiple defects.
Progestins	Virilization of female fetus.
Anrogens	Musculinization of female fetus, limb, esophageal, cardiac defect.
Tetracycline	Discolored, deformed teeth and retarded bone growth.
Warfarin	Chondrodysplasia punctata, Facial anomalies depressed nose, eye defects, hand defects and Severe anomalies of the CNS.
Carbamazepine	Craniofacial, Fingernail.
Sodium valproate	CNS defects.
Retinoic acids	Craniofacial, Cardiac, CNS defects.
Lithium	Fetal goiter, cardiac and other abnormalities.
Indomethacine and Aspirin	Premature closure of ductus arteriosus.
Isotrtinoin	Craniofacial, heart and CNS defects.
ACE inhibitors	Hypoplesia of organs, renal damage.
Alcohol	Fetal alcohol syndrome.
Phenytoin	Hypoplastic phalanges, cleft lip/palate.
Valproate	Spinal bifida and other neural tube defects
Antidepressant	Neonatal withdrawal symptoms

❖ Classification of drugs used in pregnancy:

The Food and Drug administration (FDA) classifies drugs according to the degree of risk they cause for the fetus if they are used during pregnancy.

Pregnancy Category	Category Description
Category A	• **Human:** adequate and well-controlled studies in pregnant women have no shown an increased risk of fetal abnormalities in any trimesters of pregnancy. • **Animals:** no evidence of fetal abnormalities. • **e.g.:** levothyroxine, folic acid, magnesium sulfate, liothyronine.
Category B	• **Human:** No adequate, well controlled studies demonstrate a risk to the fetus. • **Animal:** safe on the fetus of animals. • **e.g.:** metformin, hydrochlorothiazide, cyclobenzaprine, amoxicillin, pantoprazole.
Category C	• **Human:** there are no adequate and well-controlled studies in humans • **Animal:** Animal reproduction studies have shown an adverse effect on the fetusbut potential benefits may warrant use of the drug in pregnant women despite potential risks. • **e.g.:** tramadol, gabapentin, amlodipine, trazodone, prednisone.
Category D	• **Human:** there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Fetus flow up is necessary. • **e.g.:** lisinopril, alprazolam, losartan, clonazepam, lorazepam.
Category X	• **Human:** Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, drug is contraindicated in pregnant or women who may be pregnant • **e.g.:** atorvastatin, simvastatin, warfarin, methotrexate, finasteride.
Pregnancy Category	
A	**Safety established using human studies.**
B	**Presumed safety based on animal studies.**
C	**Uncertain safety, No adverse effect demonstrated in human and animal studies.**
D	**Unsafe. Evidence of risk that may in certain clinical circumstances be justifiable.**
X	**Highly unsafe. Risk of use outweighs any possible benefit.**

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